Review

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The Jumonji family: past, present and future of histone demethylases in cancer

Abstract: The first *Jumonji* gene was cloned in 1995 by Takeuchi et al. [Takeuchi T, Yamazaki Y, Katoh-Fukui Y, Tsuchiya R, Kondo S, Motoyama J, Higashinakagawa T. Gene trap capture of a novel mouse gene, jumonji, required for neural tube formation. Genes Dev 1995; 9: 1211–22.]. Several genes sharing similar biological features have since been discovered, and are currently grouped into the JMJ family. Interestingly, their deregulation has been associated with cardiac disease, obesity, neurological disorders and cancer. One of the mechanisms underlying their function is gene expression modulation via histone post-translational modifications (PTMs). Increasing evidence of *Jumonji* deregulation in tumours such as colon, prostate, haematological and breast cancer is continually emerging, hence the need to acquire a better understanding. The Genesapiens.org database of patient arrays allows target expression levels to be investigated in a wide range of cancers, corroborating and extending the role of the JMJ family. Here, we provide an overview of the expression profile and regulation of JMJ family members in cancer, examining the most recent literature in the light of analyses drawn from this database.

Keywords: cancer; chromatin-modulating drugs; epigenetics; histone demethylases; Jumonji family.

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List of abbreviations: AP1, activator protein 1; AR, androgen receptor; ALL, acute lymphoblastic leukaemia; B-ALL, B-cell acute lymphoblastic leukaemia; B-CLL, B-cell chronic lymphocytic leukaemia; DNMTs, DNA methyltransferases; NOC1b, N-oxalyl-D-cysteine 1b; HDACs, histone deacetylases; JMJs, jumonji demethylases; KDMs, lysine (K)-demethylases; NOG, N-oxalylglycine; NSCLC, non-small cell lung carcinoma; OSX, osterix; PBIT, N-phenyl-benzisothiazolinone; PHD, plant homeodomain; PHF, plant homeodomain finger; PTMs, post-translational modifications; RMS, rhabdomyosarcoma; T-ALL, T-cell acute lymphoblastic leukaemia; TS, tumour suppressor; α-KG, α-ketoglutarate.

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Introduction

It is now well established that nucleosomes are the unit of measurement for chromatin. In cells, chromatin exists in either an open or closed configuration, partially accounting for protein accessibility in nucleus (2). Recently, the scientific community has focused significant attention on the role of epigenetics in pathway regulation of healthy and diseased cells. Both differentiation of embryonic stem cell and several human diseases, including cancer and atherosclerosis, have in fact been associated with epigenetic deregulation (3–6). In contrast to genetic lesions, epigenetic changes – involving mainly cell structure and function alterations mediated by histone post-translational modifications (PTMs) – are biochemically reversible (7). Epigenetic modifications include, but are not limited to, DNA methylation, histone PTMs, nucleosome remodelling and non-coding RNAs.

DNA methylation, which occurs by the covalent modification of cytosine residues in CpG dinucleotides concentrated in so-called CpG islands (8, 9), correlates with transcriptional repression. CpG methylation pathways are altered in cancer contributing to tumour suppressor (TS) gene inactivation (10). Histone PTMs may include methylation at lysines and arginines (11), lysine acetylation, ubiquitylation and SUMOylation, or serine and threonine phosphorylation (8, 9). Lysine acetylation is often linked

to transcriptional activation, while lysine methylation is associated with activation or repression depending on location and methylation level (8, 12, 13). Chromatin modification patterns are regulated by enzymes that add (writers), remove (erasers) or read (readers) covalent modifications (5, 14, 15). Histone acetyltransferases, lysine (K)-acetyltransferases and lysine (K)-methyltransferases add acetyl and methyl groups to lysines (9). Histone deacetylases (HDACs) and histone lysine (K)-demethylases (KDMs) remove acetyl and methyl groups. Moreover, readers of epigenetic information generally possess effector domains, such as the plant homeodomain (PHD) (9). Given their deregulation in cancer and the importance of their function, HDACs and KDMs are targets for therapeutic intervention. Chemical modulation of these enzymes, mainly by inhibitors, is therefore considered a priority in cancer research. Some of these inhibitors, so-called epidrugs (drugs targeting chromatin-modulating enzymes or factors), have already been approved by the US Food and Drug Administration for the treatment of cancer (2) in some selected settings or are currently in clinical trials (16).

Here, we discuss the structure, function and deregulation in cancer of Jumonji proteins, one of the major KDM sub-families. In addition, we provide an overview of Jumonji histone demethylase-targeting molecules.

Jumonji demethylases

The JmjC family comprises 30 members that share a JmjC domain. To date, 18 of these have been shown to possess demethylase activity towards H3K4, H3K9, H3K27, H3K36 and H4K20 (8, 17–31). Based on their homology and the presence of different domains, the 30 members can be further classified into sub-families that often share substrate specificity. Figure 1 illustrates the structure, domain and known PTMs of this family based on the UniProt database (www.uniprot.org). As well as sharing a JmjC domain, all members react with α-ketoglutarate (α-KG) in an Fe(II) ion-dependent manner (Figure 2). However, not all have been shown to be catalytically active. In addition, other domains may also mediate demethylase activity independently of the JmjC domain.

Jumonji (JMJ) demethylases have been reported to act as transcriptional repressors and stimulators of cell growth, and to play a critical role in cardiac development (32). Several studies have been performed in mice with an altered expression of one of the JmjC members, including JMJD1A (JHDM2A/TSGA and KDM3A) (33–35), JMJD2A (JHDM3A and KDM4A) (36), JMJD2D (JHDM3D and KDM4D) (37), JARID1A (RBP2 and KDM5A) (37), JARID1B (PLU1 and KDM5B) (38, 39), JARID2 (JMJ) (40), JMJD6 (RDP and PTDSR1) (41–43), FBXL10 (JHDM1B and KDM2B) (44), JMJD5 (44), JMJD3 (KDM6B) (40) and UTX (40). Many different effects were observed, ranging from spermatogenetic defects (JMJD2D) (37), to obesity and male infertility (JMJD1A) (33–35), haematological and behavioural disorders (JARID1A) (29), and lethality (JMJD6) (42, 43) (JARID2) (40).

Mutations, deletions or amplifications of JmjC-containing demethylases have been associated with cancer development and aggressiveness. Moreover, FBXL10, JMJD2A, JMJD2B, JMDJ2C and JARID1B demethylases have been suggested as potential targets for cancer therapy, although the effectiveness of possible treatment and their role remain to be investigated.

Jumonji sub-families

To help avoid confusion, Table 1 provides a detailed list of gene names, symbols and synonyms currently used in the literature.

JmjC sub-family classification

FBXL family

FBXL10 (KDM2B/JHDM1B) removes methyl groups from H3K36me2/1, but not from H3K36me3. Whether FBXL10 also acts on H3K4me3 is currently debated (27, 45). In addition to the JmjC domain, this enzyme contains an F-box and two LRR domains (27). Studies have described its involvement in BLM protein mutation and its implication in lymphoma (46), as well as its silencing in human brain tumours (27). KDM2B promotes pancreatic cancer via polycomb-dependent and -independent transcriptional programs (47). In addition, data from Genesapiens.org suggest an overexpression in testicular cancer (seminoma and non-seminoma) and in B-cell acute lymphoblastic leukaemia (B-ALL), and a down-regulation in T-cell lymphoma (Figure 3).

FBXL11 (JHDM1A/KDM2A) is another member of the demethylase family, belonging to the class of H3K36me1 and H3K36me2 histone demethylases (26). This demethylase trimethylates histone residues (8, 17, 19, 20, 22, 23, 25, 29). Overexpression in non-small cell lung carcinoma (NSCLC) was shown (48). In addition, KDM2A causes

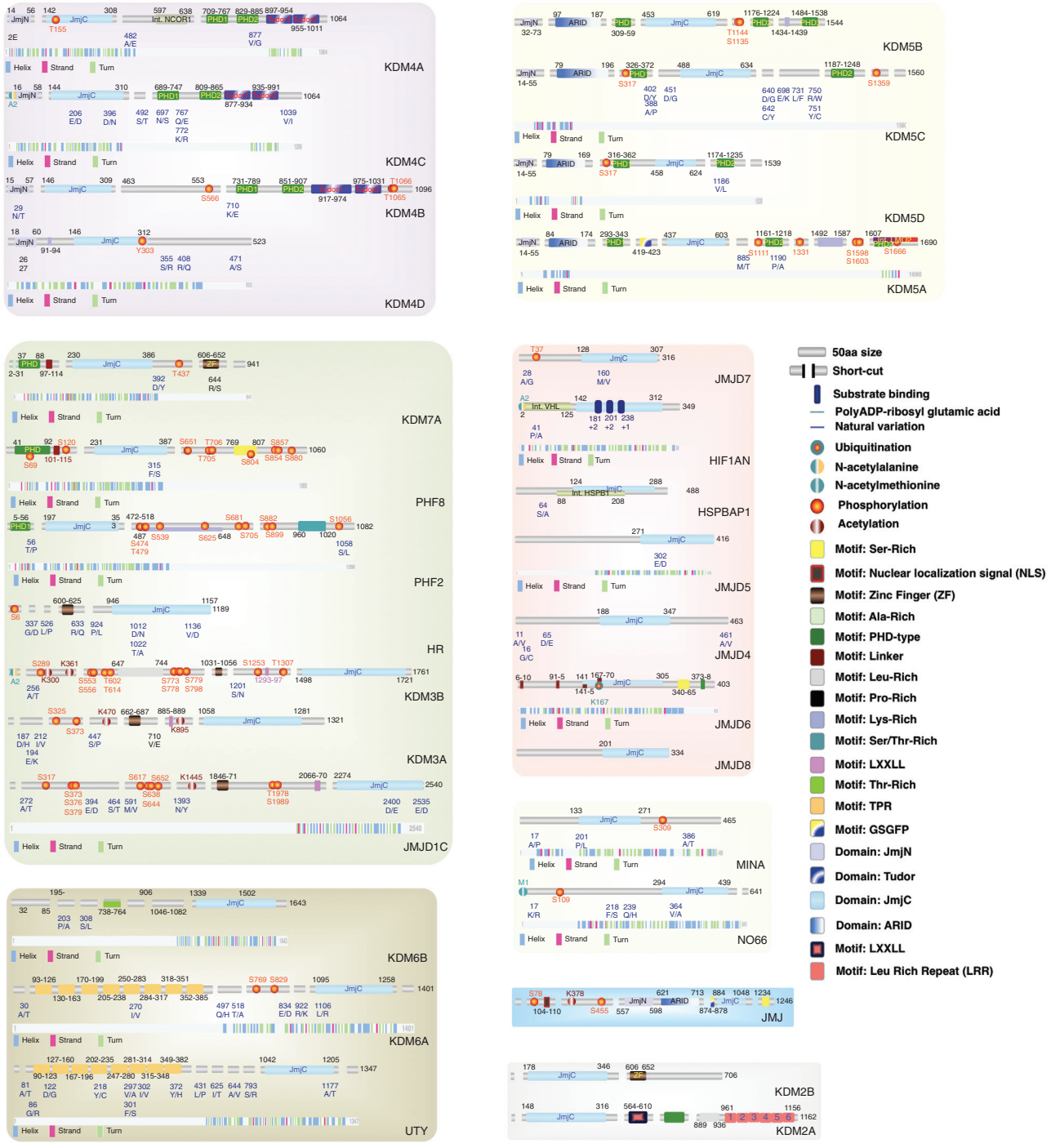

Figure 1 Schematic representation of JmjC family proteins based on UniProt database information showing structural domains, motifs, PTMs and secondary structures.

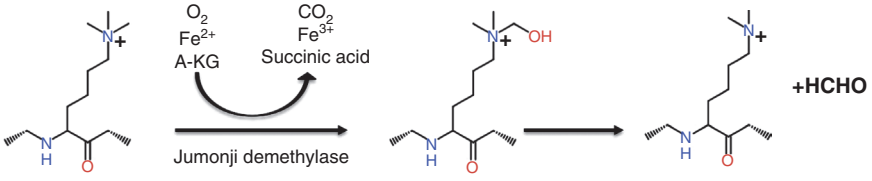

Figure 2 Jumonji demethylase reaction.

Table 1 Gene names, symbols and synonyms of JmhC proteins.

Gene name	Gene symbol	Gene synonyms
Jumonji domain containing 7	*JMJD7*	FLJ20543; FLJ20656; FLJ20807; FLJ77014; FLJ78330
Hypoxia-inducible-factor 1, alpha subunit inhibitor	*HIF1AN*	DKFZp762F1811; FIH1; FLJ20615; FLJ22027
Hairless homolog (mouse)	*HR*	ALUNC; AU; FLJ98880; HSA277165; MUHH; MUHH1
HSPB (heat shock 27kda) associated protein 1	*HSPBAP1*	FLJ22623; FLJ39386; PASS1
Jumonji, AT rich interactive domain 2	*JARID2*	**JMJ**
Jumonji C domain containing histone demethylase 1 homolog D (*Saccharomyces cerevisiae*)	*JHDM1D*	**KDM7A**; KIAA1718
Jumonji domain containing 1C	*JMJD1C*	DKFZp761F0118; FLJ14374; KIAA1380; RP11–10C13.2; TRIP8
Lysine (K)-specific demethylase 4A	*JMJD2A*	JHDM3A; JMJD2; **KDM4A**; KIAA0677
Lysine (K)-specific demethylase 4B	*JMJD2B*	FLJ44906; **KDM4B**; KIAA0876
Lysine (K)-specific demethylase 4C	*JMJD2C*	bA146B14.1; FLJ25949; GASC1; JHDM3C; **KDM4C**; KIAA0780
Lysine (K)-specific demethylase 4D	*JMJD2D*	FLJ10251; **KDM4D**; MGC141909
Lysine (K)-specific demethylase 4E	*JMJD2E*	**KDM4E**
Lysine (K)-specific demethylase 4F	*JMJD2F*	**KDM4F**
Lysine (K)-specific demethylase 6B	*JMJD3*	**KDM6B**; KIAA0346
Jumonji domain containing 4	*JMJD4*	FLJ12517; MGC129896
Jumonji domain containing 5	*JMJD5*	**KDM8**; FLJ13798
Jumonji domain containing 6	*JMJD6*	KIAA0585; PSR; PTDSR; PTDSR1
Jumonji domain containing 8	*JMJD8*	C16orf20
Lysine (K)-specific demethylase 2A	*KDM2A*	CXXC8; DKFZp434M1735; FBL11; FBL7; FBXL11; FLJ00115; FLJ46431; **JHDM1A**; KIAA1004; LILINA
Lysine (K)-specific demethylase 2B	*KDM2B*	CXXC2; Fbl10; **FBXL10**; JHDM1B; PCCX2
Lysine (K)-specific demethylase 3A	*KDM3A*	DKFZp686A24246; DKFZp686P07111; JHDM2A; JHMD2A; JMJD1; **JMJD1A**; KIAA0742; TSGA
Lysine (K)-specific demethylase 3B	*KDM3B*	5qNCA; C5orf7; **JMJD1B**; KIAA1082; NET22
Lysine (K)-specific demethylase 5A	*KDM5A*	**JARID1A**; RBBP-2; RBBP2; RBP2
Lysine (K)-specific demethylase 5B	*KDM5B*	CT31; FLJ10538; FLJ12459; FLJ12491; FLJ16281; FLJ23670; **JARID1B**; **PLU-1**; PLU1; PUT1; RBBP2H1A
Lysine (K)-specific demethylase 5C	*KDM5C*	DXS1272E; **JARID1C**; MRXJ; MRXSJ; SMCX; XE169
Lysine (K)-specific demethylase 5D	*KDM5D*	HY; HYA; **JARID1D**; KIAA0234; SMCY
Lysine (K)-specific demethylase 6A	*UTX*	bA386N14.2; DKFZp686A03225; **KDM6A**; MGC141941
MYC induced nuclear antigen	*MINA*	DKFZp762O1912; FLJ14393; MDIG; MINA53; NO52
Chromosome 14 open reading frame 169	*NO66*	C14orf169; FLJ21802; MAPJD
PHD finger protein 2	*PHF2*	GRC5; **JHDM1E**; KIAA0662; MGC176680
PHD finger protein 8	*PHF8*	DKFZp686E0868; **JHDM1F**; KIAA1111; MRXSSD; ZNF422
Ub. Transc. Tetratricopeptide repeat gene, y-linked	*UTY*	DKFZp686L12190; UTY1

The most commonly used alternative names are shown in bold.

transcriptional repression of histone deacetylase 3 (HDAC3) by removing methyl groups from dimethylated H3K36 (49).

KDM4 family

JmjC domain containing histone demethylase 3A (JHDM3A) (JMJD2A/KDM4A) is the most studied member of the KDM4 family, which includes JMJD2B (KDM4B) and JMJD2C (KDM4C). KDM4A demethylates H3K9 and H3K36, acting on H3K9me3 around 5-fold more efficiently than H3K36me3. In addition, KDM4A is more efficient in demethylating tri- as opposed to dimethylated H3K9/H3K36 (24, 25, 50). More specifically, KDM4A demethylates H1.4K26me3 (51). KDM4A can stimulate or repress gene transcription. To exert its repressive function, KDM4A is often associated with HDACs (52, 53) or with TSs such as p53 (53). Dynamic histone modifications are critical in controlling neural crest gene expression. KDM4A is expressed in forming neural folds, thus regulating neural crest formation (54). Overexpression of KDM4A may block DNA repair and induce genomic instability by suppressing the recruitment of 53BP1 and promoting tumorigenesis (51, 55). KDM4A can also inhibit Tip60 acetyltransferase, which is involved in the repair of double-stranded DNA. KDM4A interacts with activator protein 1 (AP1), which is able to regulate cell proliferation, apoptosis and differentiation. Furthermore, it

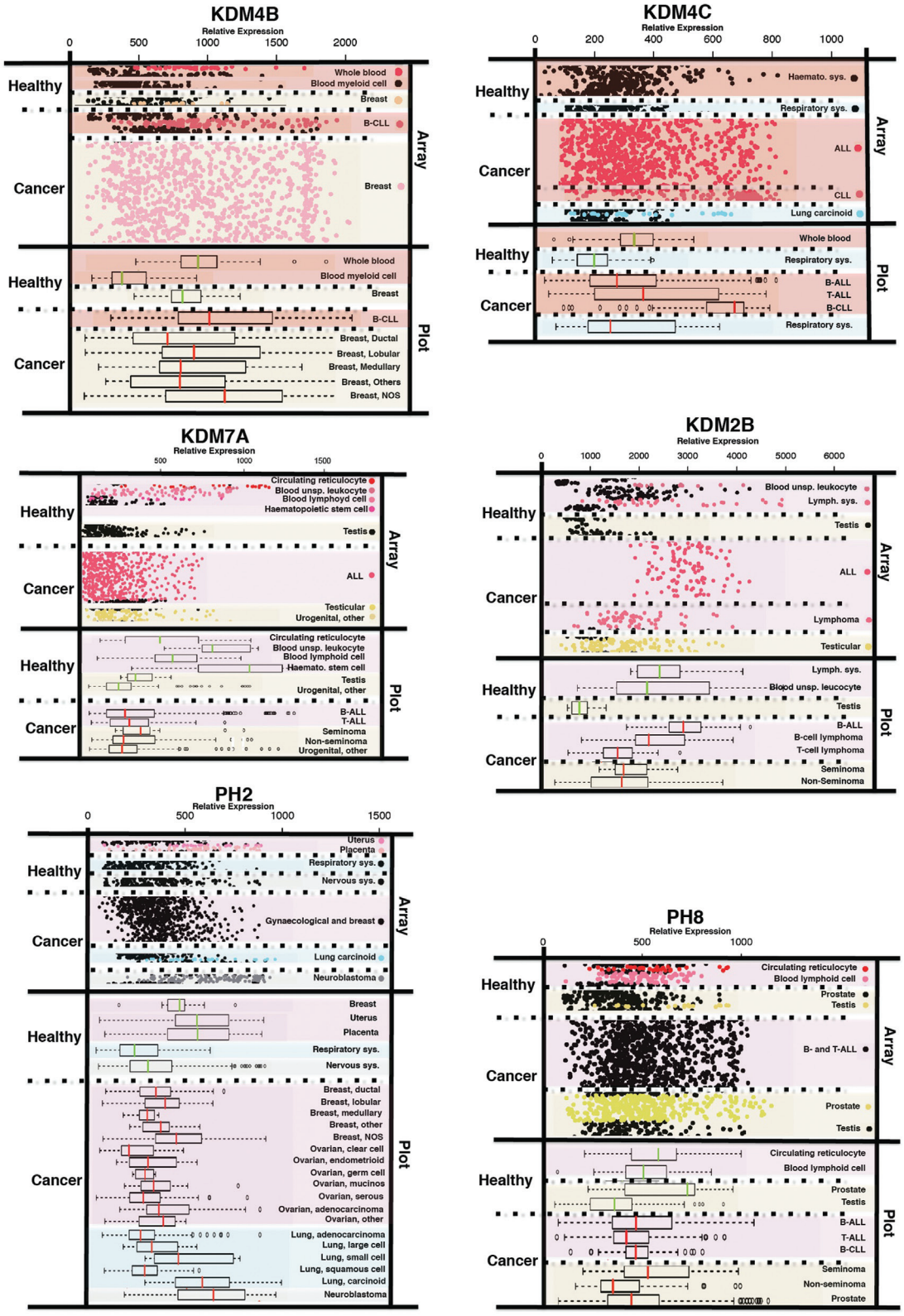

Figure 3 Significant variations in mRNA expression levels of some JmjC proteins in healthy vs. cancer patient samples array (based on the Genesapiens.org database). Dots are representative of individual array value. Box plots represent the data integration of individual experiments.

promotes AP1 binding with JUN and FOSL promoters, maintaining AP1 activation (56) and inducing cellular transformation by repression of the TS, CHD5 (57). KDM4B and KDM4C are structurally very similar to KDM4A and show similar target specificity and comparable enzymatic activity *in vitro* (50, 51). However, they may play different roles. KDM4C specifically demethylates H3K9me2 and H3K9me3 (50, 51). KDM4B and KDM4C are overexpressed in breast cancer, squamous cell carcinoma (22, 58), prostate and oesophageal cancer, and are associated with mucosa-associated lymphoid tissue lymphoma (59–61). KDM4B promotes epithelial-mesenchymal transition and consequently gastric cancer metastasis (62). Its silencing induces DNA damage response via STAT3 pathway in colorectal cancer (63). Based on data from Genesapiens.org, KDM4C seems slightly overexpressed in respiratory cancer and in B-cell chronic lymphocytic leukaemia (B-CLL). KDM4B shows up-regulation in B-CLL and deregulation in breast cancer (Figure 3). KDM4C overexpression may in fact contribute to tumour formation in ER-negative breast cancers, while KDM4B is more highly expressed in ER-positive tumour cells. Furthermore, KDM4B and KDM4C are involved in the genesis of ER-positive tumours (55) and prostate cancer (51), respectively. KDM4B is overexpressed in stomach, bladder, lung and colorectal cancers (51). The fact that KDM4C is translocated in Hodgkin's B-cells leads to its overexpression (64). Although these findings support the role of KDM4B and KDM4C as oncogenes, it is still debated whether their overexpression is a cause or consequence of tumorigenesis. KDM4C is considered to be an oncogene in many cancers, and is thus a potential target for anti-tumour epidrugs. In addition, KDM4C is able to demethylate PC2, thus promoting tumorigenesis in a potentially independent manner (64). The KDM4 family also includes JMJD2D (KDM4D), which has only been found in placental tissues (65). Bioinformatic analyses have also revealed the existence of JMJD2E (KDM4E) and JMJD2F (KDM4F), which are very similar to KDM4D (51, 66). In several studies, KDM4D has been associated with stimulation of the androgen receptor (AR) and colon cancer cell growth, suggesting its oncogenic function. KDM4D can stimulate cell proliferation and survival, indicating that it could be used as a target in anti-cancer therapy. Activation of p53 may be one of the mechanisms contrasting its pro-oncogenic functions (18). The fact that demethylation of H3K9 by KDM4D is involved in the TNF-α response (67) indicates that it may influence tumorigenesis as well as mediating inflammatory responses (67). JARID1 (KDM5) belongs to a demethylase sub-family of four members that use H3K4me2 and H3K4me3 as substrates.

KDM5 family

JARID1A (KDM5A/RBP2) is overexpressed in gastric cancer and its inhibition leads to cellular senescence of human gastric and cervical cancer cells (68). KDM5A inhibition has already been used in NSCLC models (69). The Genesapiens.org database shows that KDM5A is up-regulated in B-ALL, intestine and non-seminoma testicular cancer, while it is down-regulated in pancreatic cancer.

JARID1B (KDM5B) is highly expressed in ductal breast cancer and is associated with breast and prostate carcinomas (70, 71). KDM5B can also act as a transcriptional co-activator for AR (28, 70). KDM5B involvement in hormone signalling is consistent with high expression levels in testis, and in ovary and mammary gland of pregnant females (28).

JARID1C (KDM5C) has been implicated in X-linked pathologies (8, 72), but has also been associated with human papilloma virus tumorigenesis (73). Furthermore, KDM5C, which encodes an H3K4me2 and H3K4me3 demethylase, has been linked to embryonic development and neuronal function (74–77).

KDM6 family

UTX (KDM6A) and JMJD3 (KDM6B) remove di- and trimethyl H3K27, and contrast PcG-mediated modifications (20, 30). KDM6A is associated with MLL3/4 complexes (30, 78), and was the first demethylase found mutated in cancer. Moreover, cell proliferation and invasion are mediated by KDM6A-modulated gene expression (79, 80). Studies report that KDM6A seems to act as a TS in multiple myeloma (80). KDM6A-inactivating mutations were observed in renal carcinoma cells (81). A recent genome-wide study found RB-binding protein to be a target of KDM6A (82). The KDM6B-MLL3/MLL4 complex is involved in cell signalling pathways, including NF-κB and TGF (17, 83). KDM6B is up-regulated in prostate cancer and its expression is even higher in metastatic prostate cancer (84).

PHD finger (PHF) and zinc finger (ZF) protein family

JHDM1D (KDM7A/KIAA1718) is a member of the PHD finger (PHF) protein family, and is involved in epigenetic regulation. PHF2 recognizes histone H3K4me3 through its PHD, and this interaction is essential for histone H3K9me1 demethylation. PHF8 demethylates H4K20me1 with additional H3K9me1 and H3K9me2 demethylase activity (85). While PHF2 and PHF8 are known to be involved in

development of the neural tube and ganglia, the role of KDM7A in cancer progression remains unclear (85). Some evidence of a slight down-regulation in B-ALL and T-cell acute lymphoblastic leukaemia (T-ALL) can be found in the Genesapiens.org database. The same database shows that PHF8 is highly overexpressed in seminoma, slightly up-regulated in prostate cancer, and down-regulated in T-ALL (Figure 3). PHF2 is down-regulated in breast and ovarian cancer, but overexpressed in neuroblastoma and lung cancer (Figure 3).

A recent study showed that KDM7A suppresses cancer by acting on angiogenesis. Cancer cells expressing KDM7A appear to grow more slowly than cells in which the protein is poorly expressed. This reduction in cancer cell growth rate was associated with a decrease in formation of $CD31^+$ cells and reduced expression of multiple angiogenic factors. These findings provided the first evidence that increased expression of KDM7A suppresses cancer growth (85).

JMJD7 is a JmjC protein whose function has not yet been identified. It is thought to be a novel splice form of the phospholipase PLA2G4B, which is located downstream.

A study on acute promyelocytic leukaemia showed that KDM3B was down-regulated during differentiation through recruitment of a co-repressor complex. In addition, KDM3B suppressed differentiation of leukaemia cells, and was up-regulated in acute lymphoblastic leukaemia (ALL) patients. KDM3B might therefore play a key role in leukaemogenesis, although more studies are needed to support this preliminary hypothesis (86). Another statistical study conducted in breast cancer reported that overexpression of KDM3B/KDM5A and KDM6A is associated with improved and poor prognosis, respectively. Although these finding require further investigation, they suggest that rebalancing protein methylation levels might represent a new avenue for cancer therapy (86).

JMJD1C has been proposed as an AR co-activator (87). Recently, JMJD1C expression was found altered in breast cancer (88), and was shown to be involved in establishment of mouse lymphoid leukaemia (89).

JMJD family

JMJD6 is reported to be an arginine histone demethylase (90) and has been found increased in various human cancers. It also seems to affect alternative splicing through the regulation of splicing factors such as U2 small ribo-nucleo-protein auxiliary factor 65-kDa subunit, U2AF65 (91).

The results of a recent study investigating JMJD6 expression and its involvement in lung adenocarcinoma progression suggest that JMJD6 plays a key role and may therefore represent a new therapeutic target and prognostic marker for this tumour. A separate study identified JMJD6 as a driver in breast cancer with functional implications in tumour cell migration and growth (92).

JMJD5 (KDM8) is a histone demethylase that specifically removes methyl moieties from dimethylated lysine 36 on histone H3 and exerts a pro-proliferative effect on breast cancer cells (93). KDM8 seems to be essential during embryonic development. It also appears to act as a repressor of p53 expression, suggesting its oncogenic activity. JMJD5 is up-regulated in leukaemia and breast cancer (93). In addition, it plays an important role in cell cycle progression, circadian rhythms and embryonic cell proliferation, and has also been shown to act on H3K36me2 demethylation (94). A comparison between the structures of KDM8 and FIH, a well characterized protein hydroxylase, showed that human KDM8 may also act as a protein hydroxylase. The interaction between KDM8 and core histone octamer proteins indicates that histone proteins could be potential substrates (94).

Tetratricopeptide repeat domain (TPR) family

UTY is a UTX homolog. Both are reported as H3K27 demethylases. However, while UTX can demethylate H3K27, UTY does not seem to exert strong enzymatic action. A study conducted on mice suggests that UTX and UTY regulate gene activity through mechanisms possibly not involving demethylation (95). Another report based on the identification of differentially expressed genes related to changes in the characteristics of mouse teratocarcinoma stem cells identified several targets, including UTY, suggesting that UTY may play a key role in the early phase of mouse teratocarcinoma (96).

MINA family

MINA is involved in multiple physio- and pathological conditions, including pulmonary inflammation, cell proliferation, cancer and immunity. Levels of MINA are subject to genetic variation linked to single nuclear polymorphisms (97). Preliminary pharmacological studies suggest that MINA may regulate genes in a tissue-specific manner, but its precise role is still unclear (97).

NO66 is inhibited by osterix (OSX), a transcription factor required for osteoblast differentiation and bone formation. Decreased levels of NO66 lead to rapid differentiation of osteoblasts and bone mineralization. NO66 seems to act as an H3K4me and H3K36me demethylase *in vitro*

and *in vivo*. Interactions between NO66 and OSX regulate OSX target genes in osteoblasts by modulating methylation states (98).

To date, one study identifying two novel genes, DIRC2 and DIRC3, which span chromosome 2 and 3 breakpoints, found that the first two exons of DIRC3 can splice to the second exon of HSPBAP1, a JmjC-Hsp27 domain gene that maps proximal to the breakpoint on chromosome 3. This splice may affect normal HSPBAP1 function, concomitant chromatin remodelling, and positive stress response signals in kidney T-cells. This study therefore suggests a role for DIRC3-HSPBAP1 in familial renal cell cancer development (99).

JARID2 family

JARID2 (JMJ) is involved in rhabdomyosarcoma (RMS), which most commonly affects soft tissues in children (100). In RMS, the fusion protein PAX3-FOXO1 contributes to the phenotype of undifferentiated myogenic cells. JARID2 is overexpressed in RMS in the presence of the

Table 2 JmjC family implication in cancer.

Histone demethylase	Association with cancer
JMJD7	N.A.
HIF1AN	Hypoxia-inducible factor-1 (HIF-1) has led to an increasing understanding of the mechanism of tumour hypoxia (115)
HR	N.A.
HSPBAP1	N.A.
JARID2	Deletions of JARID2 in chronic myeloid malignancies (116). Overexpression in AML, ALL and testicular cancer (Figure 3)
JMJD1C	N.A.
JMJD2A	Silencing/down-regulation in bladder and overexpression in breast (117) cancer (118)
JMJD2B	Overexpression in malignant peripheral nerve sheath tumour (40) and B-CLL; regulation in breast cancer (Figure 3)
JMJD2C	Amplification in oesophageal cancer, breast cancer and medulloblastoma; translocation in lymphoma (40) Up-regulation in B-CLL, lung carcinoid tumour (Figure 3)
JMJD2D	Regulation in several cancers (51)
JMJD3	Regulation in breast cancer pathways. Overexpression in various cancers including lung and liver carcinomas and several haematological malignancies, primarily Hodgkin's lymphoma (40, 119–121)
JMJD4	N.A.
JMJD5	Overexpression in breast cancer (122)
JMJD6	Overexpression in poor prognostic breast and lung cancer (88, 89)
JMJD8	N.A.
KDM2A	Overexpression in NSCLC depending on cell line (48)
KDM2B	Overexpression in various leukaemias (45), and testicular cancer (47); promotion of pancreatic cancer (Figure 3)
KDM3A	Overexpression in malignant colorectal cancer, metastasized prostate adenocarcinoma, renal cell carcinoma, and hepatocellular carcinoma (40)
KDM3B	Up-regulation in ALL (92)
KDM5A	Deregulation in prostate cancer (71)
KDM5B	Overexpression in bladder, prostate and breast cancer (40)
KDM5C	Mutation in renal carcinoma (40). Depletion induces cellular senescence in human colorectal cancer (123)
KDM5D	Deletion in prostate cancer (40)
KDM7A	Regulation in ALL, and slight down-regulation in non-seminoma cancer (Figure 3)
MINA	Overpression in aggressive hepatocellular carcinoma. Significant expression in lung, and gastric cancer (124, 125)
NO66	N.A.
PHF2	Mutation or silencing/down-regulation in breast carcinoma, and head and neck squamous cell carcinoma (40) Down-regulation in breast and ovarian cancer. Overexpression including carcinoid tumour and neuroblastoma (Figure 3)
PHF8	Overexpression in prostate cancer, testis, seminoma; slight down-regulation in leukaemia (Figure 3)
UTX	Mutation in multiple tumour types including multiple myeloma, oesophageal squamous cell carcinoma, renal clear cell carcinoma, transitional cell carcinoma, and chronic myelomonocytic leukaemia; overexpression in breast cancer (40)
UTY	N.A.

N.A., indicates that findings are not yet well reported.

PAX3-FOXO1 complex. Moreover, higher JARID2 levels are associated with metastasis independently of the state of the fusion protein. JARID2 therefore seems to act as a direct transcriptional target of the fusion protein PAX3-FOXO1 and as a downstream effector of PAX3-FOXO1, able to maintain a non-differentiated myogenic phenotype in RMS. Thus, JARID2 may represent a therapeutic target for the treatment of RMS patients (100).

To date, JARID1D, HR, HSPBAP1, JMJD7, HIF1AN, JMJD5, JMJD4, JMJD8, KDM3B, JMJD1C, UTY, MINA AND NO66, and JARID2 (Figure 1; Table 1) have been poorly correlated with cancer in literature.

Using the Genomatix software (www.genomatix.de), we summarised signal transduction pathway associations and potential interactions implicated in diseases involving JmjC family members (Table 2).

Targeting Jumonji demethylases with epidrugs: a window on the future

While targeting of HDACs and DNA methyltransferases (DNMTs) has advanced to the stage where drugs have entered the clinic, only a limited number of anti-cancer drugs against Jumonji demethylases have been developed (none of which have reached clinical trials). KDM inhibitors include molecules that act preferentially on KDM4A and KDM3A sub-families. Based on the finding that Jumonji demethylases exploit $Fe2^{+}$ and α-KG as cofactors to catalyse demethylation, an α-KG analogue, N-Oxalylglycine (NOG) (Figure 4A,B) was generated and used *in vitro* (22), showing a weak inhibition of KDM4A and KDM4C (22). Another α-KG analogue inhibitor, the oncometabolite hydroxyglutarate (Figure 4C), targets KDM4A, KDM4C and KDM2A (101). Recently, hydroxamic acids were identified as JMJD2 demethylase inhibitors (102). For example, caffeic acid (Figure 4D) seems to non-selectively inhibit KDM4C, and also acts on HDACs and DNMTs. A series of N-oxalyl-D-tyrosine derivatives were investigated for the inhibition of KDM4 (103). In addition, 4-hydroxypyrazole A (Figure 4E) inhibits KDM4C. A hydroxamate analogue based on the crystal structure of KDM4A (Figure 4F) acts as a more potent inhibitor (104). In addition, a selective JMJD2 inhibitor able to modulate cell growth in oesophageal carcinoma was synthesized and tested (105). Compounds that remove the zinc ion, including disulfiram and ebselen, inhibit JMJD2A (105). JMJD2A was also found to be specifically inhibited by the disruption of its zinc binding site (105).

Various inhibitors have been created based on N-Oxalyl-D-Cysteine 1b (NOC1b), a NOG analogue which seems to inhibit both JMJD2E and KDM4A (106). GSK-J1 (Figure 4G) is a small molecule that targets KDM6B, while GSK-J4 is another drug that appears to block pro-inflammatory cytokines produced by human macrophages (107).

The structure of KDM6A was defined by X-ray crystallography (108), leading to the design of a small molecule that acts by inhibiting KDM6A (108). Initial studies on this inhibitor demonstrated that it reduces the production of pro-inflammatory cytokines by macrophages, a process that depends on both KDM6B and UTX. Recently, Daminozide (Figure 4H) was found to be a selective inhibitor of JHDM1B and PHF8 (107).

Progress towards the development of potent inhibitors for the Jumonji family is very slow because of the

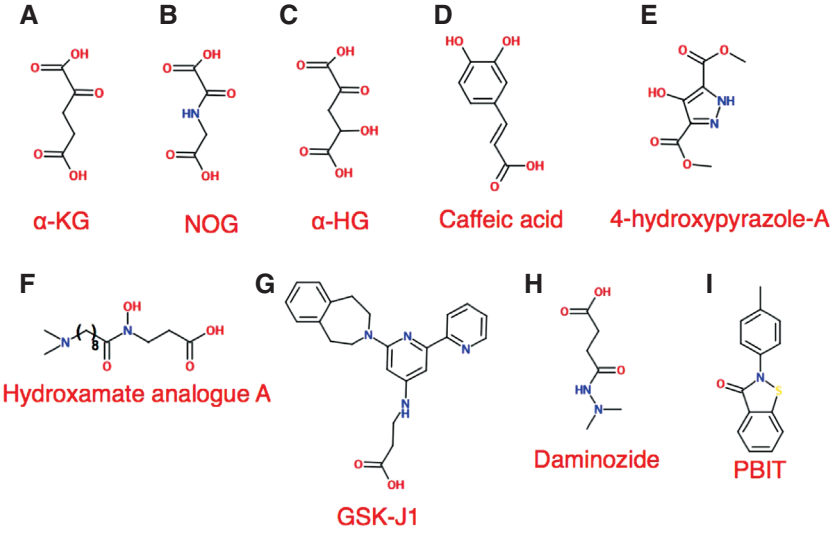

Figure 4 Chemical structure of JmjC inhibitors.

Table 3 Signal transduction pathway associations and potential interactions of JmjC proteins in human diseases.

Pathway component	Signalling pathway
HIF1AN	
HIF1A (115)	Hypoxia-inducible-factor-1, alpha subunit (basic helix-loop-helix transcription factor) (Genomatix BioCarta)
NOTCH (116)	Notch (Genomatix BioCarta STKE KEGG)
PI3K (117)	Phosphatidylinositol (Genomatix BioCarta STKE KEGG)
PKC (117)	Protein kinase c (Genomatix BioCarta)
VEGF (117)	Vascular endothelial growth factor (Genomatix BioCarta KEGG)
JMJD6	
APOPTOSIS (42, 118)	Apoptosis
RAC (119)	Small gtp binding protein rac (Genomatix BioCarta KEGG)
TFRC (120)	Transferrin receptor (p90, cd71) (BioCarta)
KDM2B	
ANTIAPOPTOTIC (121)	Antiapoptotic
APOPTOSIS (45)	Apoptosis
NFKB (45)	Natural factor kappa b (Genomatix BioCarta)
PROLIFERATION (45)	Proliferation
RB1 (45)	Retinoblastoma 1 (Genomatix BioCarta)
TP53 (45)	Tumour protein p53 (Genomatix BioCarta BioCarta)
KDM2A	
NFKB (122)	Natural factor kappa b (Genomatix BioCarta)
KDM6B	
CDKN2 (123)	Cyclin-dependent kinase inhibitor 2
GSK (124)	Glycogen synthase kinase (Genomatix BioCarta)
IL4 (125)	Interleukin 4 (Genomatix BioCarta)
NFKB (124)	Natural factor kappa b (Genomatix BioCarta)
ONCOGENIC (123)	Oncogenic
PKC (126)	Protein kinase c (Genomatix BioCarta)
SMAD (125)	Mothers against dpp homolog (Genomatix BioCarta STKE KEGG)
STAT (127)	Signal transducer and activator of transcription (Genomatix BioCarta STKEK EGG)
TP53 (128)	Tumour protein p53 (Genomatix BioCarta)
C14ORF169	
PROLIFERATION (129)	Proliferation
JARID2	
PROLIFERATION (129, 130)	Proliferation
DIFFERENTIATION (131)	Differentiation
NOTCH (132)	Notch (Genomatix BioCarta STKE KEGG)
KDM5B	
E2F1 (133)	e2f transcription factor 1 (Genomatix BioCarta)
PROLIFERATION (133)	Proliferation
RB1 (133)	Retinoblastoma 1 (Genomatix BioCarta)
SMAD (116)	Mothers against dpp homolog (Genomatix BioCarta STKE KEGG)
TGF BETA (116)	Tgf beta (Genomatix BioCarta BioCarta STKE KEGG)
KDM5C	
SMAD (134)	Mothers against dpp homolog (Genomatix BioCarta STKE KEGG)
TGF BETA (134)	Tgf beta (Genomatix BioCarta STKE KEGG)
KDM5A	
IGF1 (69)	Insulin-like growth factor 1 (Genomatix BioCarta)
PHF8	
DEVELOPMENTAL (135)	Developmental
HR	
WNT (136)	Wingless type (Genomatix BioCarta STKE KEGG)
KDM3A	
HIF1A (137)	Hypoxia-factor-1, alpha subunit (basic-helix-loop-helix transcription factor) (Genomatix BioCarta)
MAPK (138)	Mitogen-activated protein kinase (Genomatix BioCarta STKE KEGG)
SPRY (138)	Sprouty homolog (drosophila) (Genomatix BioCarta)

lack of structural information. KDM4 family inhibitors will likely require a much more detailed chemical and biochemical analysis and longer preclinical trials. Although several chemically different inhibitors have been proposed, X-ray crystal structures of at least some Jumonji targets have demonstrated an indirect effect, likely mediated by alteration of complex composition (41, 109–111). The availability of other X-ray crystal structures will represent a crucial step in the development of novel Jumonji modulators. More potent and selective inhibitors of histone demethylases are expected to be synthesized in the coming years (112–114). Recently, KDM5B inhibitors have been developed, including N-Phenyl-Benzisothiazolinone (PBIT) (Figure 4I). This molecule is able to inhibit JARID1 and KDM5B, but not KDM6B and UTX. Further investigations are required to clarify the mechanism of PBIT inhibitors. A molecule called JIB-04 specifically inhibits Jumonji histone demethylase activity in cancer (115), and acts only on tumour cells, blocking their vitality. This small molecule may therefore represent an important tool for treatment of breast cancers overexpressing Jumonji demethylases with significantly lower survival rates (115, 116) (Table 3).

Summary and outlook

Histone modifications are key epigenetic mechanisms modulating fate decisions both in healthy and diseased cells. Epigenome-based deregulations, together with genome alterations, causally contribute to tumorigenesis. The scenario in cancer is highly complex. On one hand there exists a plethora of alterations that can progress throughout malignancy and may crosstalk with each other. On the other hand, the context cannot be 'generalized': cancer should be considered as 'a disease of the individual' and treatments should be (or should become) as tailored as possible. Emerging high-throughput sequencing technologies applied to cancer provide a valuable tool to allow the personalized study of 'individual' diseases. The fact that chromatin-modulating enzymes can be pharmacologically targeted makes them an exciting field of innovative intervention in human diseases, including cancer.

At this stage, pharmacological modulation is very complex as interference with so-called 'readers' might prove to be much more difficult than canonical competitive inhibition. An additional level of complexity is given by the fact that epigenetic-based deregulations are generally marked by protein complexes, and epidrugs may likely indirectly influence the content of these regulators. Convincing evidence of the deregulation of histone demethylases, including the Jumonji family, indicates that they may undoubtedly become important diagnostic and prognostic tools.

However, Jumonji-targeting drugs acting in the low micromolar range or selective for specific enzymes are still required. The growing body of knowledge within the scientific community needs to be supported by greater mechanistic insights. To date, it is still unclear whether pure epigenetic effects are beneficial against cancer. The difficulty in both defining a hierarchy of effects and understanding causal roles of some anti-cancer readouts adds still further complexity. Only a long-term approach will help to distinguish more precisely between cause and effect, and to clarify some of the current issues.

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