The language of chromatin modification in human cancers

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Abstract | The genetic information of human cells is stored in the context of chromatin, which is subjected to DNA methylation and various histone modifications. Such a 'language' of chromatin modification constitutes a fundamental means of gene and (epi)genome regulation, underlying a myriad of cellular and developmental processes. In recent years, mounting evidence has demonstrated that miswriting, misreading or mis-erasing of the modification language embedded in chromatin represents a common, sometimes early and pivotal, event across a wide range of human cancers, contributing to oncogenesis through the induction of epigenetic, transcriptomic and phenotypic alterations. It is increasingly clear that cancer-related metabolic perturbations and oncohistone mutations also directly impact chromatin modification, thereby promoting cancerous transformation. Phase separation-based deregulation of chromatin modulators and chromatin structure is also emerging to be an important underpinning of tumorigenesis. Understanding the various molecular pathways that underscore a misregulated chromatin language in cancer, together with discovery and development of more effective drugs to target these chromatin-related vulnerabilities, will enhance treatment of human malignancies.

In eukaryotes, chromatin is organized in the repeated units of nucleosomes, each composed of a histone octamer and a piece of surrounding DNA. Histone post-translational modifications (PTMs) and DNA methylation create chromatin variations[1,2]. Besides the core replicative histones (that is, H2A, H2B, H3 and H4), histone variants also exist and are assembled into nucleosomes in a replication-independent manner. Some of the better-studied histone lysine methylations occur predominantly on histones H3 and H4, including histone H3 lysine 4 (H3K4), lysine 9 (H3K9), lysine 27 (H3K27), lysine 36 (H3K36), lysine 79 (H3K79) and histone H4 lysine 20 (H4K20). Each of these lysines can exist in four methyl states — unmodified, monomethylated (Kme1), dimethylated (Kme2) and trimethylated lysine (Kme3); alternatively, they can exist in acetylated or other acylated forms yielding staggering complexity, although the abundance and relative weight of various PTMs in terms of function can vary (Supplementary Fig. 1a). In mammalian cells, DNA modifications are mainly 5-methylcytosine (5mC) and its oxidative derivatives, which all have a role in gene or genome regulation[3,4]. These chromatin variations establish a fundamental means of regulating essentially all the DNA-templated processes such as gene transcription, DNA replication, DNA damage repair and DNA recombination.

Histone PTMs and DNA methylation, established and removed by antagonizing enzymes of writers and erasers, respectively (FIG. 1a), regulate chromatin-based processes both in *cis* and in *trans*. In *cis*, histone PTMs change structural or physical properties of nucleosomes, for example, increasing DNA accessibility or neutralizing the negative charge of DNA via histone charge-altering modifications (for example, acetylation and phosphorylation). In *trans*, chromatin modification serves as a context-dependent docking site for recruiting readers or other effectors[1]. It is worth noting that a good number of writers and erasers also harbour a chromatin reader module, thereby opening up various possibilities for potential crosstalk among chromatin modifiers including self-propagation, cooperation, competition or antagonism. Writers, erasers and readers can also potentially target nonhistone proteins to regulate their respective functions[5–8].

A wealth of evidence now supports an intimate relationship between chromatin misregulation and cancer. In this Review, we discuss recent advances that illustrate how a range of mechanisms lead to a misregulated 'language' of chromatin modifications, profoundly affecting cancer initiation and progression. Owing to the prevalence and impact of chromatin deregulation, a mechanistic understanding of this process in cancer will ideally lead to the development of promising therapeutics.

Chromatin misregulation in cancer

As an extension to our previous review of the topic[9], we wish to further develop and expand the notion of a misregulated chromatin language by first covering

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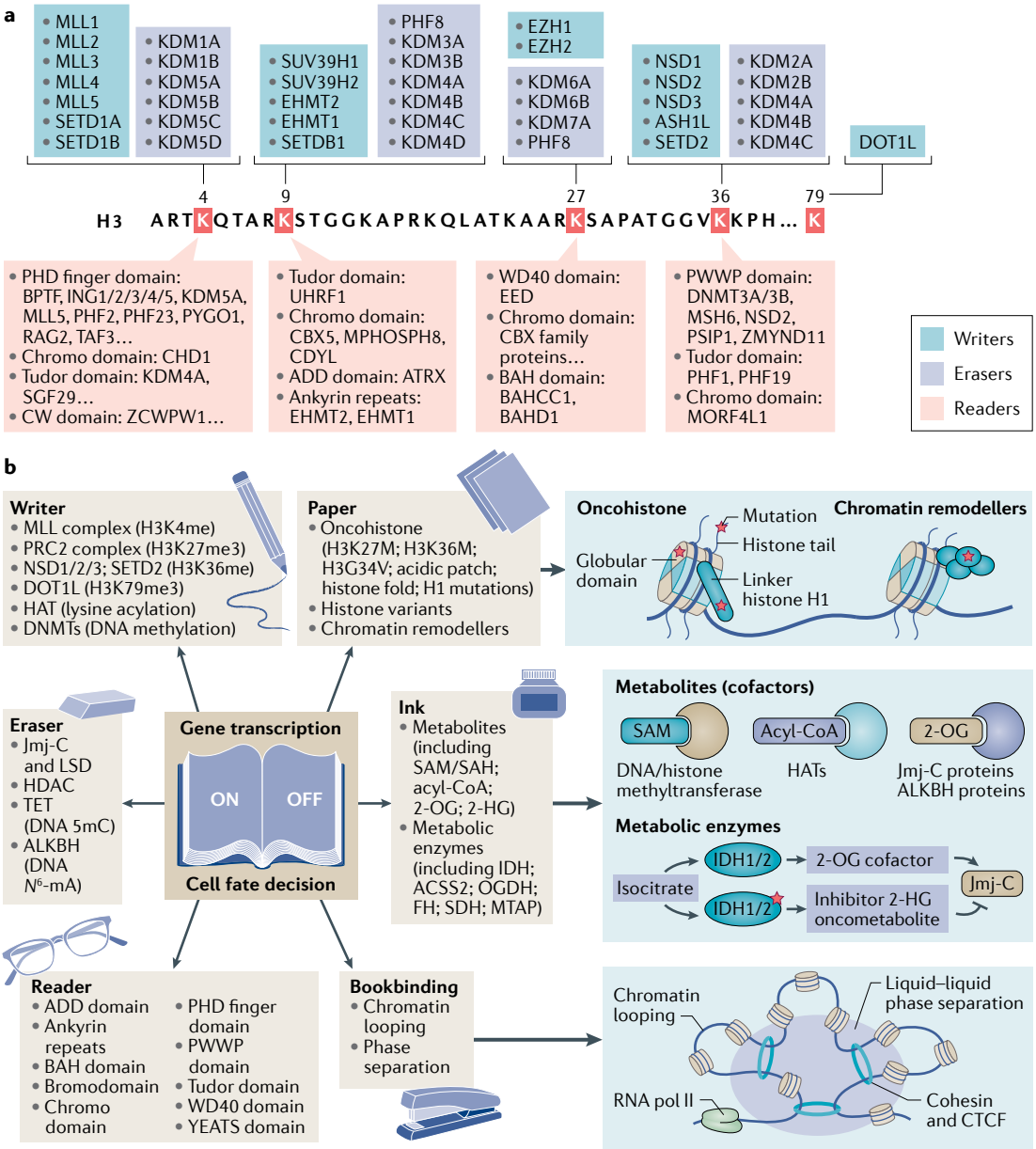


Fig. 1 | **The misregulated 'language' of chromatin modification in cancer. a** | Overview of certain key writers, erasers and readers of histone H3 methylations at K4, K9, K27, K36 and K79. Note that this list is not exclusive; many other modifications such as acetylation, phosphorylation, ubiquitylation and arginine methylation also occur in all histones[262], which are not shown in the figure. **b** | A misregulated language of chromatin modification underlies oncogenesis. In addition to cancer-related mutations of chromatin modification writers, erasers or readers, the oncohistone and chromatin remodeller mutations alter numerous fundamental aspects of chromatin, as illustrated by the 'paper' that the 'language' of chromatin modification operates on. Moreover, cellular metabolites and oncometabolites form essential cofactors for erasers, and also represent the 'paint and ink' used by writers (and in some cases erasers) to modify histones and DNA. A versatile set of readers allow cells to recognize and engage various chromatin marks such as lysine methylation, acetylation, crotonylation and more. Similar to a process of stapling and bookbinding, chromatin looping and phase separation-based regulation are involved in the high-order organization of chromatin and regulation of the (epi)-genome, processes frequently altered in cancers. Altogether, a collection of deregulated mechanisms converge, resulting in a misregulated chromatin language. 2-HG, 2-hydroxyglutarate; 2-OG, 2-oxoglutarate; DNMT, DNA methyltransferase; EZH2, enhancer of Zeste homologue 2; HAT, histone acetyltransferase; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; Jmj-C, Jumonji C; MLL, mixed lineage leukaemia; N^6-mA, DNA adenine methylation; PHD, plant homeodomain; PRC2, Polycomb repressive complex 2; RNA Pol II, RNA polymerase II.

cancer-related alterations of DNA methylation and cell metabolism (FIG. 1b). Much evidence shows that various metabolic pathways generate metabolites, such as acetyl-CoA, *S*-adenosylmethionine and lactate, that serve as cofactors for chromatin writer enzymes to deposit their respective chemical tags onto the chromatin[10,11]. In addition, metabolites such as α-ketoglutarate and NAD^+ are essential cofactors for certain chromatin

Polycomb repressive complex 2
(PRC2). Complex consisting of core subunits EZH2 or EZH1, EED, SUZ12 and RbAp46 or RbAp48, which catalyses the methylation of histone H3K27.

SWI/SNF chromatin remodelling complex
Comprising approximately 15 subunits, uses the energy from ATP hydrolysis to mobilize nucleosomes.

erasers[10,11]. As a hallmark of cancer, altered cell metabolism can therefore cause perturbations in the chromatin state, leading to deregulation of gene expression[10,12–14]. Furthermore, it is increasingly clear that a versatile set of reader domains evolve as a 'toolkit' for cells to sense and recognize the previously less-studied chromatin PTMs such as lysine crotonylation (Kcr) or benzoylation[15–17]. Therefore, in addition to the fact that cancers frequently carry mutations of chromatin writers, readers or erasers, an excess or lack of metabolites and/or their misuse can equally contribute to the misregulation of chromatin modification (FIG. 1b), thereby profoundly shaping cancer pathogenesis[10,12–14].

An unexpected finding of studies based on data from The Cancer Genome Atlas is the identification of recurrent oncogenic somatic mutation of histones, also known as oncohistones[18] (BOX 1), across cancer types including glioma[19], sarcoma[20] and lymphoma[21]. Studies of the most common oncohistones have convincingly shown that histone mutations alter epigenomic patterning, affecting DNA-templated processes such as gene transcription and DNA damage repair. A common theme of classic H3 tail oncohistones is the functional inhibition of cognate histone writers to which oncohistones bind, leading to perturbation of epigenetic and transcriptomic states. H3 oncohistones have been reviewed in detail elsewhere[18–20,22,23].

Mutations within chromatin remodelling complexes represent another class of cancer-related lesions, which are estimated to affect about 10–20% of all cancers[24]. Similar to oncohistones, deregulation of chromatin remodellers is known to alter the accessibility of chromatin, leading to chromatin 'openness' versus 'compaction', and may additionally crosstalk with other chromatin modifiers, as exemplified by antagonism between the Polycomb repressive complex 2 (PRC2) and the SWI/SNF chromatin remodelling complex[25,26]. Thus, recurrent oncohistone and chromatin remodeller mutations constitute an important mechanism by which tumours alter the normal process of chromatin-based gene and genome regulation, to gain growth advantages.

Emerging evidence from in vitro studies now demonstrates that phase separation, a phenomenon of molecule compartmentalization without subcellular membranes (BOX 2), is critically involved in assembly of chromatin itself and chromatin-associated factors; this phase

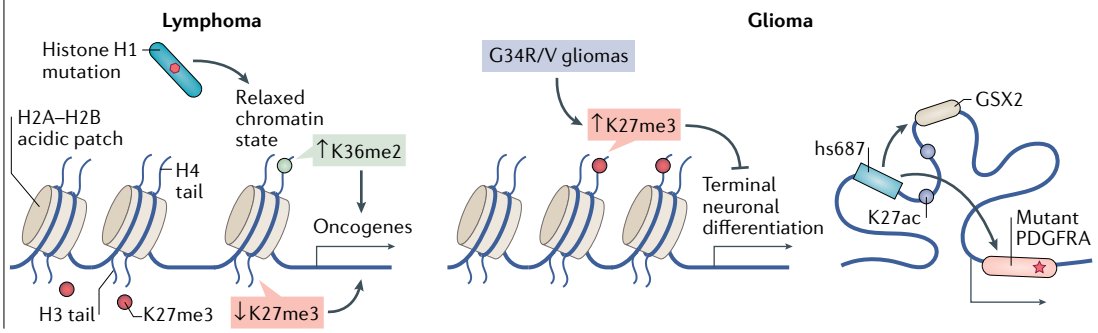
Box 1 | **Oncohistones**

Histone missense mutations were recurrently detected in cancers and thus named oncohistones. Certain oncohistones including H3K27M, H3K36M and H3G34V/R/W/L mutations are common in paediatric cancers[263]. Recently, oncohistone sites have been expanded from histone tails to globular domains and linker histones[18]. For example, while the mutations of H2B (E71Q or E76Q) and H4 (D68Y/N/H and R92T) are predicted to disrupt the H2B–H4 binding interface, those of histone H2A (E56Q, E92D/K) and H2B (E113K/Q) occur in the 'acidic patch', a regulatory interface on the histone 'disc' surface essential for binding of chromatin regulators[264]. Approximately 60 nonsynonymous mutations of linker histone H1 were detected in human lymphomas[265]. Recently, two studies have shown that depletion of linker H1 histones in mice (which mimics their loss-of-function mutations found in patients with lymphoma) caused chromatin decompaction and an increase in H3K36me2 levels with concurrent decrease in H3K27me3 levels, ultimately leading to transcriptional activation of lymphoma-related oncogenes[21,33] (see figure). Many oncohistones are tumour type-specific, influencing histone modification patterns globally. Although it only accounts for 3–17% of total H3, H3K27M has a dominant effect[266].

The mechanisms underlying oncohistone-induced oncogenesis are complex. A simple model is that oncohistones influence histone methyltransferases in *trans* or in *cis*[263]. H3K9M, H3K27M and H3K36M were reported to inhibit their corresponding lysine methyltransferases in *trans*. This explains the globally decreased H3K27me3 or H3K36me3 seen in the H3K27M- or H3K36M-mutant cells. Dominant effects of H3K27M and H3K36M also support the in *trans* inhibition model. Histone H3G34 mutations inhibit H3K36me2/3 methyltransferases in *cis*: only nucleosomes containing H3G34 mutations exhibit the decreased H3K36me2/3 (REF.[266]). In addition, the H3.3G34R/V mutations found primarily in glioma also lead to globally elevated levels of H3K27me3, which impede neuronal differentiation; an aberrant chromatin looping brings a *cis*-regulatory element of GSX2 (hs687) in proximity to the promoter of platelet-derived growth factor receptor-α (*PDGFRA*), thereby facilitating the expression of mutant PDGFRα during gliomagenesis (see figure)[34,267–269].

Effects of oncohistones are complex and content dependent. For example, although global H3K27me3 loss is observed in H3K27M-mutant cells, a striking gain of H3K27me3 was identified at certain genomic loci[270,271]. Elevated H3K27ac and global DNA hypomethylation are observed in H3K27M-mutant tumours[266,270,271], indicating complex crosstalk between different chromatin modifications.

We hypothesize that 'oncohistones' at core and linker histones cause chromatin deregulation, which involves the perturbed functionality of writers, readers or erasers, (de-)compaction of chromatin and structural alteration of nucleosomes.



Box 2 | **Chromatin phase separation**

Liquid–liquid phase separation (LLPS) compartmentalizes biochemical reactions without subcellular membranes. LLPS is driven by multivalent nonspecific ionic and hydrophobic interactions, and relies on the polymeric nature and intrinsically disordered regions of macromolecules[30]. Chromatin is composed of repeated nucleosomes with disordered histone tails. Recent studies demonstrate that the chromatin itself can form liquid droplets in vitro and in the nucleus[30]. Other transcription machineries such as RNA polymerase II, mediators such as MED1 and transcription factors also have intrinsically disordered regions and are regulated by phase separation[272,273].

The phase separation behaviour of chromatin is regulated by many factors such as histone H1, histone tails, linker DNA and nucleosome dynamics[30]. Histone modifications and reader proteins also directly regulate chromatin phase separation. Histone acetylation itself antagonizes chromatin LLPS[30], whereas multi-bromodomain proteins form multivalent interactions with acetylated chromatin and facilitate LLPS of chromatin[30]. Transcriptional coactivators BRD4 and MED1 mediate LLPS at superenhancer regions[274]. Heterochromatin regions also form nuclear puncta mediated by H3K9me3 and its reader, chromobox protein homologue 5 (CBX5; also known as HP1α)[28,31]. CBX5 binds to H3K9me3 and recruits the H3K9me writer SUV39H1 and scaffold protein TRIM28 (REF.[275]). This multi-subunit complex forms condensed macromolecule-enriched droplets and can exclude DNase or general transcription factors[275].

In recent years, more and more epigenetic factors have been reported to form separated phases, and this property is directly related to human diseases. For example, mutations of ENL promote its phase separation behaviour and activate oncogene expression in Wilms tumour[169].

separation-based regulation is proposed to be vital for establishment not only of appropriate chromatin modification patterning but also of 3D organization of chromatin[27–31]. In addition, chromatin loops can connect the spatially distal enhancer and promoter, thereby modulating transcription (FIG. 2a). It is conceivable that misregulation of chromatin looping and 3D organization represent vital oncogenic pathways leading to epigenomic and gene deregulation. In support of this, an oncogenic gain-of-function (GOF) mutation of enhancer of Zeste homologue 2 (EZH2), an H3K27me3 writer, was recently reported to induce structural changes in 3D chromatin structure and long-range chromatin interactions[32]. Furthermore, while loss-of-function (LOF) mutation of histone H1 was shown to alter the 3D chromatin architecture during lymphomagenesis[21,33], the H3.3-G34R/V oncohistone establishes aberrant chromatin looping and a permissive chromatin environment for transcriptional activation of platelet-derived growth factor receptor-α (*PDGFRA*), an oncogene frequently mutated in glioma[34]. Collectively, these examples highlight the connection between histone modifications, oncohistones and chromatin high-order structures.

Phenotypic and functional heterogeneity of human cancers is well documented, and intratumoural epigenomic heterogeneity leads to considerable variation among tumour cell subpopulations[35]. In addition, epigenetic plasticity results in tumour cell adaption and resistance to therapeutic treatment, which represents a huge challenge in the clinic[36,37]. Indeed, misregulation of DNA and histone modifications can be as frequent as, if not more frequent than, gene mutations, contributing to cancer heterogenicity[36–38].

‘Miswriting’ of chromatin modifications

Recent studies have gained important insights, partly via cryogenic electron microscopy structures, into how multi-subunit writer machineries deposit their respective modifications[39,40]. Although chromatin modification potentially affects numerous gene targets, a common theme is that miswritten chromatin modifications exert their oncogenic effects more heavily by deregulating one or a few sets of crucial nodes, notably those genes that regulate stemness, cell cycle and antitumour immunity, among others[9,41]. In addition to the better-studied PTMs, several others, such as lysine lactylation (Supplementary Fig. 1a), have been newly identified, providing new connections between metabolic malfunction and chromatin deregulation[42].

Deregulation of histone acylations, beyond acetylation. Histone lysine acetylation (Kac) positively regulates gene transcription by promoting DNA accessibility and, importantly, creating a docking site for reader proteins. Histone acetylation can be catalysed by three major families of histone acetyltransferases (HATs), namely the GCN5-related *N*-acetyltransferase (GNAT), EP300 and related CREB-binding protein (CREBBP; also known as CBP), and MYST families. Because of a close relationship between histone acetylation and transcriptional activation, malfunction of HATs often perturbs appropriate gene-expression programmes, leading to development of disease[43–45].

Numerous reported cases exist in the literature illustrating how deregulation of histone acetylation writers contributes to oncogenesis. For example, the MYST family proteins, KAT8 (also known as MOF) and KAT7 (also known as HBO1), were recently demonstrated to be oncoproteins in the setting of acute leukaemias, with their in vivo leukaemogenic functions dependent on the acetyl-‘writing’ activity harboured within the HAT domain[46,47]. MacPherson et al.[47] showed that KAT7 and associated complex components are essential for inducing histone H3 lysine 14 acetylation (H3K14ac) in leukaemia-initiating stem cells (LSCs) and that H3K14ac facilitates the processivity of RNA polymerase II to maintain the high expression of proto-oncogenes such as *HOXA9* and *HOXA10*, an event that can be targeted by inhibition of KAT7.

Another prominent example of pro-oncogenic deregulation by chromatin writers comes from inactivating mutations of *CREBBP* or *EP300*, which together account for approximately 60–70% of follicular lymphomas (FLs) and 25–30% of diffuse large B cell lymphomas (DLBCLs)[48,49] and represent a common, early event during pathogenesis of these lymphomas (FIG. 2a). Aside from haematological cancers, mutations of HATs such as EP300 were also reported in patients with solid cancers such as glioma and melanoma[44,45]. Somatic mutations within *EP300* or *CREBBP* are predominantly truncation and missense substitutions clustered within the HAT domain, which impair writing of acetyl onto chromatin. Studies in mouse models demonstrated that *Crebbp* deletion alone results merely in hyperplasia but is able to cooperate with deregulated anti-apoptotic protein BCL-2 to cause a spectrum of fully penetrant tumour phenotypes that resemble human diseases[50–52]. These findings establish CREBBP as a bona fide tumour suppressor in lymphomagenesis[49–53]. Mechanistically, *CREBBP* mutation in germinal centre (GC) B cells causes a range of

Germinal centre (GC) B cells
B cells residing in the GC sites of secondary lymphoid organs such as spleen and lymph nodes where B cells proliferate, differentiate and mutate the antibody-encoding genes (through somatic hypermutation) to generate antibodies of higher affinity during the immune response.

epigenetic, transcriptomic and cell microenvironment perturbations. These include aberrant silencing of genes involved in cell differentiation, cell cycle control and immune response, mediated partly by an onco-repressor complex of HDAC3–BCL-6–NCOR2 (also known as SMRT); the enhanced MYC signalling and immune evasion were both observed in these lymphoma animal models, contributing to tumorigenesis[50–55]. In lymphoma, a large proportion of perturbations that involve CREBBP or EP300 loss occurs at gene enhancers, resulting in unopposed histone deacetylation, and *CREBBP* mutation often coexists with inactivation of mixed lineage leukaemia 4 (MLL4; also known as KMT2D) or MLL3 (also known as KMT2C) (FIG. 2a), another class of histone writers functioning at enhancer chromatin[56,57]. Together, this indicates synergy between the two lesions in causing epigenetic perturbation.

HATs may also cooperate with oncoproteins. For example, the HATs KAT2A (also known as GCN5) and KAT5 (also known as TIP60) both act as coactivators of MYC and are crucially involved in MYC-driven transcriptional activation and oncogenesis[8,58–62]. Additionally, direct acetylation of the MYC protein by HATs can regulate its protein stability[60].

Advances in high-sensitivity mass spectrometry permit identification of short-chain acylation of histone lysines, such as crotonylation and 2-hydroxyisobutyrylation[15] (Supplementary Fig. 1a). In cells, a combination of acetylation and acylations, rather than a single type, are often used by HATs to 'mark' target genes[15]. Non-acetyl histone acylations are generally correlated with gene activation but can be functionally distinct from acetylation[15]. Moreover, histone lysine lactylation, generated from either exogenous or endogenous lactate, was identified as a new acylation that regulates the expression of homeostatic genes[42]. Cancer cells generate energy predominantly through aerobic glycolysis followed by lactic acid fermentation, a metabolic alteration known as the Warburg effect[63]. It is therefore conceivable that miswriting of these histone lysine lactylations may link the Warburg effect with gene expression alterations in cancer, which merits further investigation.

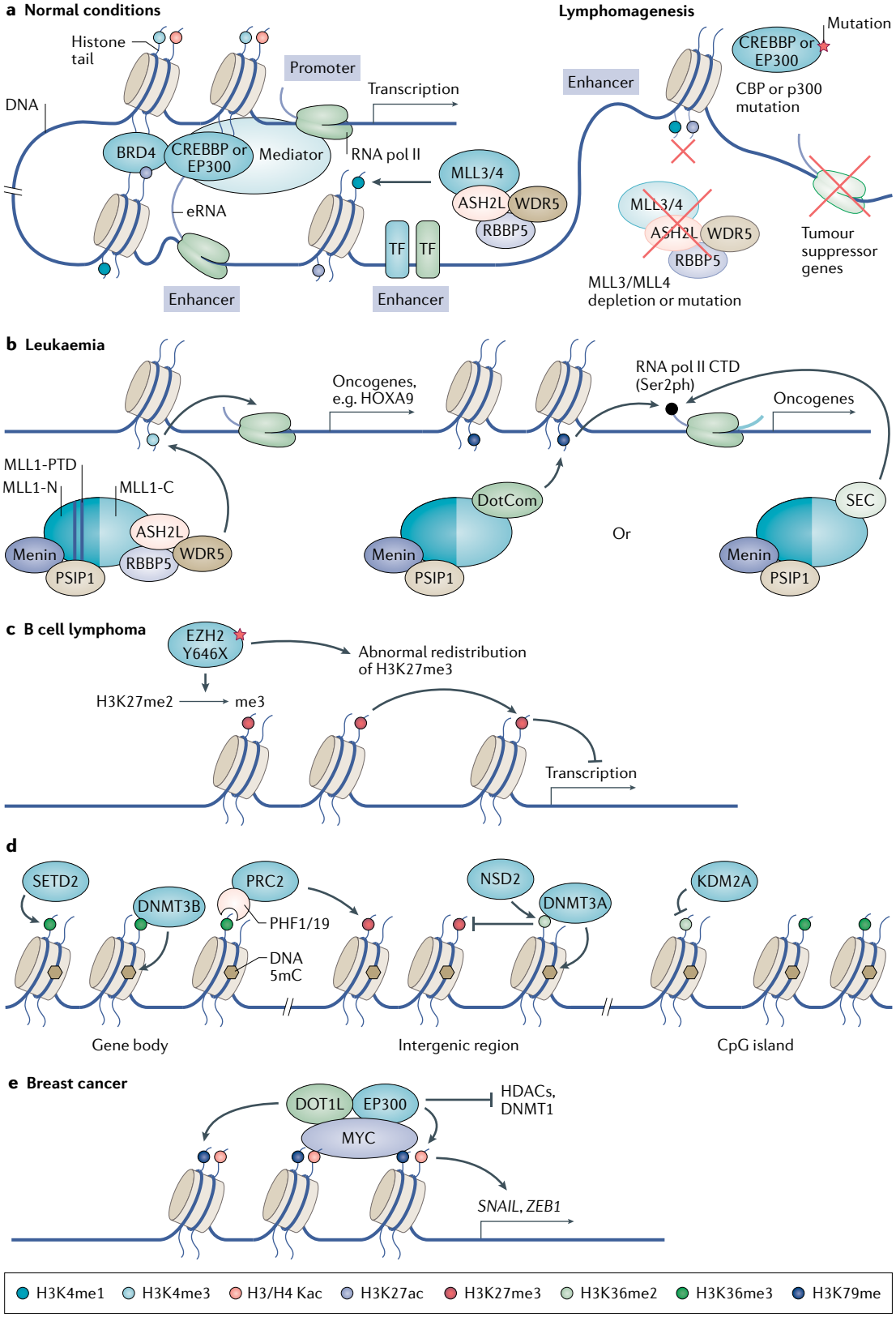
MLL mutation and deregulation of H3K4. Members of the MLL family of lysine methyltransferases (also known as the KMT2 family) activate transcription partly via writing H3K4 methylation at gene promoters and enhancers. The N terminus of MLL1 (also known as KMT2A) physically interacts with cofactors required for genomic targeting such as menin and PC4 and SFRS1-interacting protein (PSIP1; also known as LEDGF)[64,65], whereas the C-terminal SET domain of MLL1 associates with WDR5, RBBP5 and ASH2L to establish a highly ordered catalysis centre to mediate histone methylation[66,67] (FIG. 2b). Structures of MLL1 complexes and their interactors were recently solved (Supplementary Fig. 1b,c), which revealed that binding of RBBP5 and ASH2L stabilizes an active conformation of MLL1 and that the subsequent MLL1 binding to histone H3 substrates induces a conformational change of the catalytic centre, presenting H3K4 to the catalytic pocket[68]. The MLL1 complex engages mononucleosomes by interacting with both nucleosomal DNA and histone H4 (REFS[69,70]) (Supplementary Fig. 1b). Overall, the activity and chromatin targeting of MLL1 methyltransferase is delicately regulated by its physical interaction and crosstalk with cofactors, as well as the chromatin context.

Rearrangement of the *MLL1* gene in acute myelogenous leukaemia (AML) or acute lymphoblastic leukaemia (ALL) provides a classic example of how miswriting of histone methylation causes oncogenesis[71–73]. As a common form of MLL1 rearrangement, MLL1 fusion essentially replaces the MLL1 C-terminal segment with one of the fusion partners, many of which recruit gene-activating machineries such as super elongation complex (SEC) and/or the H3K79 methyltransferase, DOT1L. More than 100 MLL1 fusion partners have been reported to date, with the most frequent being AF4, ENL, AF9, AF10 and ELL[71,72,74]. Recruitment of DOT1L, SEC and other coactivators (such as wild-type MLL1 and PAF1) by the MLL1 fusion protein establishes a self-reinforcing gene-activation network, resulting in abnormal potent transcription of leukaemia-related oncogenes such as HOX family genes and *MEIS1* (REFS[71,72,75]) (FIG. 2b). Partial tandem duplication of MLL1, the other type of MLL1 rearrangement occurring in approximately 5–10% of AMLs, generates in-frame partial duplication of an N-terminal regulatory region of MLL1, resulting in aberrant elevation of H3K4me3 and histone acetylation at oncogenes such as *HOXA9* (REFS[76,77]). Whereas MLL1 rearrangement acts as a GOF mutation to promote acute leukaemias, its family members often function as tumour suppressors in other cancers[73]. Moreover, mutations of MLL family genes also exist widely among solid cancers such as lung cancer and breast cancer[73,78].

LOF mutation of *MLL3* and *MLL4*, the two main writers of enhancer-associated H3K4me1 (REF.[79]), is frequent in a range of cancers such as FL, DLBCL, lung cancer and melanoma[57,78,80–82]. In normal cells, MLL3 and MLL4 assemble complexes for establishing H3K4me1 at target enhancers or superenhancers, promoting transcription of genes related to differentiation or tumour suppression such as tumour necrosis factor-α-induced protein 3 (*TNFAIP3*) and suppressor of cytokine signalling 3 (*SOCS3*)[78,81,83]. Besides core subunits (WDR5, ASH2L and RBBP5), MLL3 also interacts with BAP1, a histone H2A deubiquitinase and tumour suppressor that is required for recruiting MLL3 to enhancers[84]. Mutational hotspots have been reported to occur within the sequence encoding the plant homeodomain (PHD) finger of MLL3, which mediates BAP1 interaction. Mutations in this region disrupted BAP1 binding, resulting in a defective recruitment of MLL3 to enhancers of tumour suppressor genes[84]. Additionally, the MLL3 complex interacts with KDM6A (also known as UTX), an H3K27me3-specifc demethylase frequently mutated in cancer[57,85]. Thus, MLL3 inactivation induces an increase in H3K27me3 at tumour suppressors[84]. Altogether, *MLL3* and *MLL4* mutations provide an example of enhancer-specific histone modification leading to enhancer malfunction and, subsequently, cancerous transformation.

Acylation
A chemical process of transferring an acyl group to the substrate. It includes but is not limited to acetylation.

Superenhancers
Chromatin regions that comprise multiple enhancers and are enriched in transcription factors and mediators.



Mutation of PRC2 and the miswritten pattern of H3K27me3. Trimethylation of H3K27 is catalysed by PRC2, which is composed of EZH2, Polycomb proteins SUZ12 and EED, and histone-binding protein RBBP7 or RBBP4. Deregulation of EZH2, the catalytic subunit of PRC2, is intimately associated with cancer development[86,87]. Intriguingly, EZH2 has both oncogenic and tumour-suppressive functions under different contexts, highlighting a multifaceted function[86,87].

Approximately 20% of patients with B cell lymphoma (FL and DLBCL) and 3% of patients with melanoma harbour a heterozygous hotspot mutation of *EZH2* within

◀ Fig. 2 | **Miswriting of chromatin modification promotes oncogenic development.** **a** | An active enhancer is marked by H3K4me1 and H3K27ac, which are generated by mixed lineage leukaemia 3 (MLL3) and MLL4, and histone acetyltransferases such as CREB-binding protein (CREBBP) and EP300. Enhancers are bound by transcription factors (TFs), mediators and transcription coactivators such as BRD4, which activate RNA polymerase II (RNA pol II) for mediating productive transcription from promoters and generating enhancer RNA (eRNA) to facilitate gene activation. Enhancer–promoter looping underlies activation of gene transcription. Loss or inactivation mutation of *CREBBP* or *EP300* and/or *MLL3* or *MLL4* is characteristic of cancers such as B cell lymphoma, resulting in decreased H3K27ac and/or H3K4me1 at enhancers and reduced expression of genes related to tumour suppression, cell differentiation and/or antitumour immunity. **b** | Wild-type MLL1 uses an N-terminal region for interacting with chromatin-binding cofactors, menin and PC4 and SFRS1-interacting protein (PSIP1). MLL1 or its partial tandem duplication (PTD) results in elevated H3K4me3 at oncogenes such as HOX, promoting acute leukaemogenesis. An MLL1 fusion oncoprotein gains a C-terminal segment from its fusion partner, such as AF9, ENL or AF4, which recruits DOT1L complex (DotCom) for catalysing H3K79 methylation and/or the super elongation complex (SEC) for catalysing serine 2 phosphorylation (Ser2ph) of the C-terminal domain (CTD) of RNA pol II. H3K79me and RNA pol II CTD Ser2ph, possibly with other activators such as PAF1, promote expression of oncogenes such as those of the HOX family. **c** | A collective action of wild-type EZH2 and its gain-of-function mutation, Y646X (X = F, C, H, S or N), causes abnormal elevation of H3K27me3 in lymphoma, leading to downregulation of transcripts related to cell cycle control and B cell differentiation. **d** | Regulatory roles of H3K36me2/3 modifications at gene body, intergenic regions and CpG islands. First, intergenic H3K36me2, installed by NSD family proteins, and SETD2-mediated H3K36me3 at gene body both antagonize H3K27me3. Meanwhile, H3K36me2/3 serves as a docking site for the DNA methyltransferase 3A (DNMT3A) DNMT3B PWWP domain, resulting in co-localization of H3K36me2/3 with DNA 5-methylcytosine (5mC) at gene body and intergenic regions. Additionally, recognition of H3K36me3/2 by the Tudor domain of plant homeodomain (PHD) finger protein 1 (PHF1) or PHF19 provides a possible mechanism for the Polycomb repressive complex 2 (PRC2) to establish de novo H3K27me3. Deregulation of NSD family proteins, SETD2, PRC2, PHF1/19 and DNMT3A is frequent in various human tumours. **e** | In breast cancer, overexpressed DOT1L interacts with MYC and EP300 to antagonize histone deacetylases (HDACs) and DNMT1, leading to the elevated H3K79me and H3Kac levels at epithelial–mesenchymal transition (EMT)-promoting oncogenes such as SNAIL and ZEB1.

the catalytic domain residue Tyr646 (Y646X, where X is F, C, H, S or N)[88–90]. In wild-type cells, activity of PRC2 is tightly regulated and inversely correlated to the degree of methylation at H3K27; the catalytic efficiency of PRC2 is greatest in converting H3K27me0 into H3K27me1, and dramatically diminished in subsequent methylation reactions[86,89]. However, lymphomas additionally produce a PRC2 that contains mutant EZH2-Y646X, which displays an altered substrate preference. PRC2 with EZH2-Y646X shows greatly enhanced catalysis in converting H3K27me1 or H3K27me2 into higher methylation states[86,89]. As a result, the two forms of PRC2 carrying wild-type EZH2 or EZH2-Y646X act in concert to increase global H3K27me3 in cancer[86,89] (FIG. 2c). Two relatively rare EZH2 mutations, A677G and A687V found in 1–3% of lymphomas, have a similar GOF effect to EZH2-Y646X[86]. In mouse models, EZH2-Y646F promotes pathogenesis of lymphoma[91] or melanoma[90] in the presence of a coexisting oncogene, such as an activating mutation in *BCL2* or *BRAF*. In lymphoma, wild-type and mutant EZH2 together repress transcription of cell cycle inhibitors (such as *CDKN2A* and *CDKN1A*) and transcription factors required for post-GC B cell development (such as *IRF4* and *PRDM1*)[91–93].

EZH2 also controls genes related to tumour immunity. In particular, wild-type EZH2-induced H3K27me3 acts to repress expression of CXC-chemokine ligand 9 (*CXCL9*) and *CXCL10* within tumours[94], as well as transcripts related to major histocompatibility complex class 1 antigen processing[95], uncovering a role for EZH2 in tumour immune evasion. Additionally, EZH2-Y646F perturbs the interaction between GC B cells and immune cells (such as the requirement for T cell help) in mouse models and helps establish a niche for promoting malignant transformation of GC B cells[96]. Thus, EZH2 regulates a battery of transcripts related to cell cycle control, cell differentiation, antitumour immunity and tumour cell microenvironment.

In addition to the oncogenic GOF mutations in *EZH2* that are seen in lymphoma and melanoma, LOF mutations of PRC2 components such as *EZH2*, *EED* and *SUZ12* are prevalent among many other cancers including myeloid neoplasms, T cell ALL (T-ALL) and malignant peripheral nerve sheath tumours[97–99]. A tumour-suppressive role of PRC2 was indeed substantiated by recent investigations of mouse knockout models in which abolition of PRC2 function promoted progression of cancers such as leukaemia and malignant peripheral nerve sheath tumour[100,101]. Structural characterization of PRC2 provides important molecular explanations of how certain missense mutations detected in cancers can influence PRC2 activity[102–104]. EZH2, EED and SUZ12 form a 'core' complex with wide-ranging interactions[102,103] (Supplementary Fig. 1d). It should be noted that EED contains a 'reader' domain to bind H3K27me3 or trimethylation of JARID2 (a PRC2 cofactor), an event that mediates allosteric activation of PRC2 (REF.[103]) (Supplementary Fig. 1d). Interestingly, a number of cancer-related mutations of PRC2 precisely target those residues involved in either the H3K27me3-'reading' domain of EED or the stimulatory responsive motif of EZH2, all of which interfere with allosteric activation of PRC2 (REFS[104,105]). Together, an exquisite regulation of PRC2 and 'writing' of H3K27me3 are critically involved in appropriate control of gene expression and tumour–microenvironment interaction, two processes frequently deregulated during oncogenesis.

H3K36me2 and H3K36me3 miswriting underscores development of certain cancers. Deregulation of H3K36me2 and H3K36me3 is now appreciated to be pivotal in a wide range of human cancers[106,107]. Although they differ by just one methyl group, H3K36me2 and H3K36me3 have distinct genomic localizations, writers and biological functions[106]. Whereas H3K36me3 is predominantly located within the body of actively transcribed genes, H3K36me2 is enriched in intergenic regions[106]. The histone-lysine *N*-methyltransferase SETD2 (also known as KMT3A) is the only identified enzyme catalysing H3K36me3, whereas H3K36me2 can be generated by a diverse set of writers including the histone lysine methyltransferases NSD1, NSD2, NSD3 and ASH1L[39]. Under different contexts, H3K36 methyltransferases can be oncogenic or tumour suppressive. For example, whereas SETD2 acts as a tumour suppressor in acute leukaemia, T cell lymphoma, lung cancer and renal cancer[106], gene rearrangement and/or GOF mutation of NSD2 occurs frequently in multiple myeloma and paediatric ALLs, resulting in globally elevated H3K36me2 levels and enhanced tumorigenicity

in vitro and in vivo[106–109]. In a subset of AMLs, abnormal fusion between NUP98, a nucleoporin protein, and a C-terminal SET domain-containing segment of NSD1 or NSD3 is sufficient to drive AML development by activating proto-oncogenes such as those of the HOX gene family[110]. Furthermore, inactivating mutations in NSD1 were found at a frequency of 5–15% in several types of epithelial cell cancer[106,111,112], suggesting a general relevance of H3K36 miswriting in oncogenesis.

Mechanistically, H3K36 di- or tri-methylation (H3K36me2/3) modulates various processes, such as mRNA splicing, DNA damage repair and gene transcription, and profoundly shapes epigenomic landscapes of cancer cells, notably H3K27me3 and DNA methylation[106] (FIG. 2d). An antagonistic effect of H3K36me2/3 on PRC2 restricts deposition and/or spreading of H3K27me3 (REFS[113–117]). Additionally, H3K36me2/3 is recognized by a Pro-Trp-Trp-Pro (PWWP) 'reader' module harboured within the DNA methyltransferases (DNMTs) DNMT3A and DNMT3B, thereby regulating the chromatin localization of these methyltransferases and resultant de novo DNA methylation[118–120]. In support of this, cancers with NSD1 or NSD2 deregulation are characterized by DNA hypomethylation and/or a miswritten H3K27me3 pattern[108,111,113,115,121]. Furthermore, recent studies have illustrated the structural basis of NSD3 engagement with the nucleosomal substrate and also showed that overexpression and/or GOF mutation of NSD3 drives lung squamous cell carcinoma (LUSC) in both genetically engineered mouse models and patient-derived xenograft models[122,123]. Specifically, NSD3 interacts extensively with nucleosomal DNA, histone H3 and histone H2A (Supplementary Fig. 1e), which facilitates the active conformation of NSD3 (REF.[122]). GOF mutation of NSD3 (such as T1232A) enhances its H3K36me2-writing activity, significantly contributing to development and progression of LUSC in vivo[123]. Mechanistically, NSD3 GOF mutation potentiates the oncogenic gene-expression programme, notably MYC targets and mTOR signalling, in a catalytic activity-dependent manner[123].

Deregulation of DOT1L and H3K79 methylation influences histone acetylation. DOT1L is the only methyltransferase known to write H3K79 methylation. In addition to its oncogenic role whereby it interacts with MLL fusion proteins, DOT1L promotes oncogenesis by antagonizing histone deacetylation. In breast cancer, DOT1L overexpression is correlated with poorer prognosis, and a complex of DOT1L, MYC, CREBBP and EP300 activates genes related to epithelial–mesenchymal transition (EMT)[124]. Mechanistically, recruitment of DOT1L and the resultant H3K79 methylation repel histone deacetylase 1 (HDAC1) and DNMT1 from EMT-regulatory genes, thereby promoting breast cancer progression[124] (FIG. 2e). Likewise, DOT1L antagonizes the histone deacetylase sirtuin 1 (SIRT1) in MLL-rearranged leukaemia and HDAC1 in thymic lymphoma[125,126]. However, the molecular underpinnings of such an antagonism and acetylation state switch remain to be further determined.

Structural studies of DOT1L in complex with nucleosome (Supplementary Fig. 1f) revealed how DOT1L activity is (de)regulated[127–131]. DOT1L binds to the nucleosome via multivalent interactions with the histone H4, the nucleosome acidic patch, nucleosomal DNA and mono-ubiquitylated histone H2B lysine 120, which together stabilize the active conformation of DOT1L and augment its enzymatic activity. DOT1L binding also induces a conformational change of histone H3, reorienting H3K79 from an inner position to the catalytic centre[130]. A recent work further delineated a role for histone H4 lysine 16 acetylation (H4K16ac), a characteristic of open, transcriptionally permissive chromatin, in direct stimulation of Dot1, the yeast homologue methyltransferase of DOT1L[132]. Structural studies also reveal how MLL fusion recruits DOT1L — the leucine zipper of AF10, a common MLL fusion partner, is complexed with a coiled-coil region of DOT1L, forming a parallel coiled-coil dimer through various hydrophobic interactions[127] (Supplementary Fig. 1g). Mutations at the AF10–DOT1L interaction interface abrogated leukaemogenicity of MLL1–AF10 in cell models[127]. MLL also forms oligomers with AF10 through coiled-coil interactions and potentiates leukaemogenenesis[133] (Supplementary Fig. 1g). Thus, in addition to directly targeting DOT1L with available catalytic inhibitors, inhibiting DOT1L binding to nucleosome or cofactors may represent an alternative therapeutic strategy.

DNA methylation is frequently miswritten in cancer. DNMTs establish 5mC, which modulates characteristics such as gene expression, mRNA splicing and genome stability[4]. A well-known characteristic of almost all tumours is global hypomethylation and concurrent abnormal hypermethylation at localized sites such as CpG islands[134]. Although the mechanisms underlying this deregulated 5mC pattern in cancer are likely complex and remain elusive, recent studies suggested an involvement of the ubiquitin-like with PHD and ring finger domains protein 1 (UHRF1), a multifaceted E3 ligase that not only interacts with DNMT1, a writer of maintenance DNA methylation, but also 'reads' various chromatin modifications including hemi-methylated CpG, H3K9me3 and H3K18 and H3K23 ubiquitylation at replication forks[135–138]. In colon and liver cancers, UHRF1 overexpression is a predictor of poor clinical outcomes and, intriguingly, exerts dual effects on DNA methylation patterning[136]. Specifically, while UHRF1 overexpression in the zebrafish liver was sufficient to induce global DNA hypomethylation[136], presumably via reduction of DNMT1 levels, UHRF1 also contributed to sustained aberrant promoter hypermethylation at tumour suppressor genes and promoted tumorigenesis in xenograft models of liver and colon cancers[136,137]. Interplay between UHRF1, DNMT1, replication fork machinery and chromatin is complicated, warranting further investigation[136–139].

Another recently appreciated example that highlights a close relationship between 5mC miswriting and oncogenesis comes from DNMT3A, a de novo DNMT frequently mutated in haematological malignancies such as AML and premalignant disorders such as clonal haematopoiesis[140–144]. Somatic mutations of DNMT3A in haematopoietic stem or progenitor cells

De novo DNA methylation
DNA methylation occurring at previously unmethylated sites.

Acidic patch
A negatively charged region in nucleosome, formed by six residues from H2A and H2B.

CpG islands
Genomic regions (typically 300–3,000 bp) that are highly enriched for CpG dinucleotides and usually lack DNA methylation.

Maintenance DNA methylation
DNA methylation that is maintained based on the existing template DNA methylation.

Clonal haematopoiesis
A phenomenon of the expansion of a clonal blood cell population with the same genetic mutation.

represent an early premalignant event; mutations are clustered at DNMT3A functional domains including the catalytic domain and protein–protein interaction interfaces, with a noted mutational hotspot at Arg882. In haematopoietic stem or progenitor cells, loss of DNMT3A or introduction of a hotspot mutation (such as R882H in human or R878H in mouse DNMT3A) predominantly causes CpG hypomethylation at gene-regulatory elements such as enhancers, leading to potentiation of gene-expression programmes related to stemness[145–153]. Acquisition of additional oncogenic mutations, such as those of a proliferative kinase and/or nucleophosmin (*NPM1*), is required for progression into full-blown cancer[145–153].

DNMT3A uses its homodimeric interface, a target recognition domain (TRD) and a catalytic loop for mediating multivalent[154] interactions with CpG-containing DNA duplex[155,156] (Supplementary Fig. 1h,i). A set of haematological cancer-related DNMT3A alterations is spatially clustered at the substrate-binding interface of DNMT3A as exemplified by V716D, R792H and K841E, which interfere with activity of wild-type DNMT3A in a dominant-negative fashion[155]. Intriguingly, structural analyses permit valuable insights into the mutational hotspot of DNMT3A — its R882 residue forms interactions with both DNA substrate and the TRD loop (Supplementary Fig. 1i), a DNMT3A motif crucially involved in engaging CpG dinucleotides[155]. A hotspot mutation such as R882H enhances dynamics of the TRD loop and compromises both the activity and CpG specificity of DNMT3A[155,157,158]; conceivably, non-CpG methylation by R882H-mutated DNMT3A can potentially be immediately eliminated during replication, as DNMT1, the enzyme responsible for maintenance DNA methylation, shows strict CpG specificity[157]. R882-mutated DNMT3A also displays altered preference for CpG-flanking sequences[157,159,160]. Together, this suggests that premalignant or malignant haematological cells harbouring the R882-mutated DNMT3A predominantly display a CpG hypomethylation phenotype and that the effect of DNMT3A hotspot mutation on CpG methylation is hypomorphic.

Misinterpretation of chromatin modifications

Specific histone modifications are recognized by specific readers. For example, bromodomains are classic histone acetylation readers and anticancer drug targets[161]. Following the discovery of bromodomains, double PHD finger domain and YEATS domains were also identified as histone acetylation readers[162,163]. In this section, we discuss recent advances that illustrate how improper interpretation of chromatin marks due to deregulation of chromatin readers represents a pivotal pathway leading to oncogenesis, indicative of attractive drug targets for therapeutics.

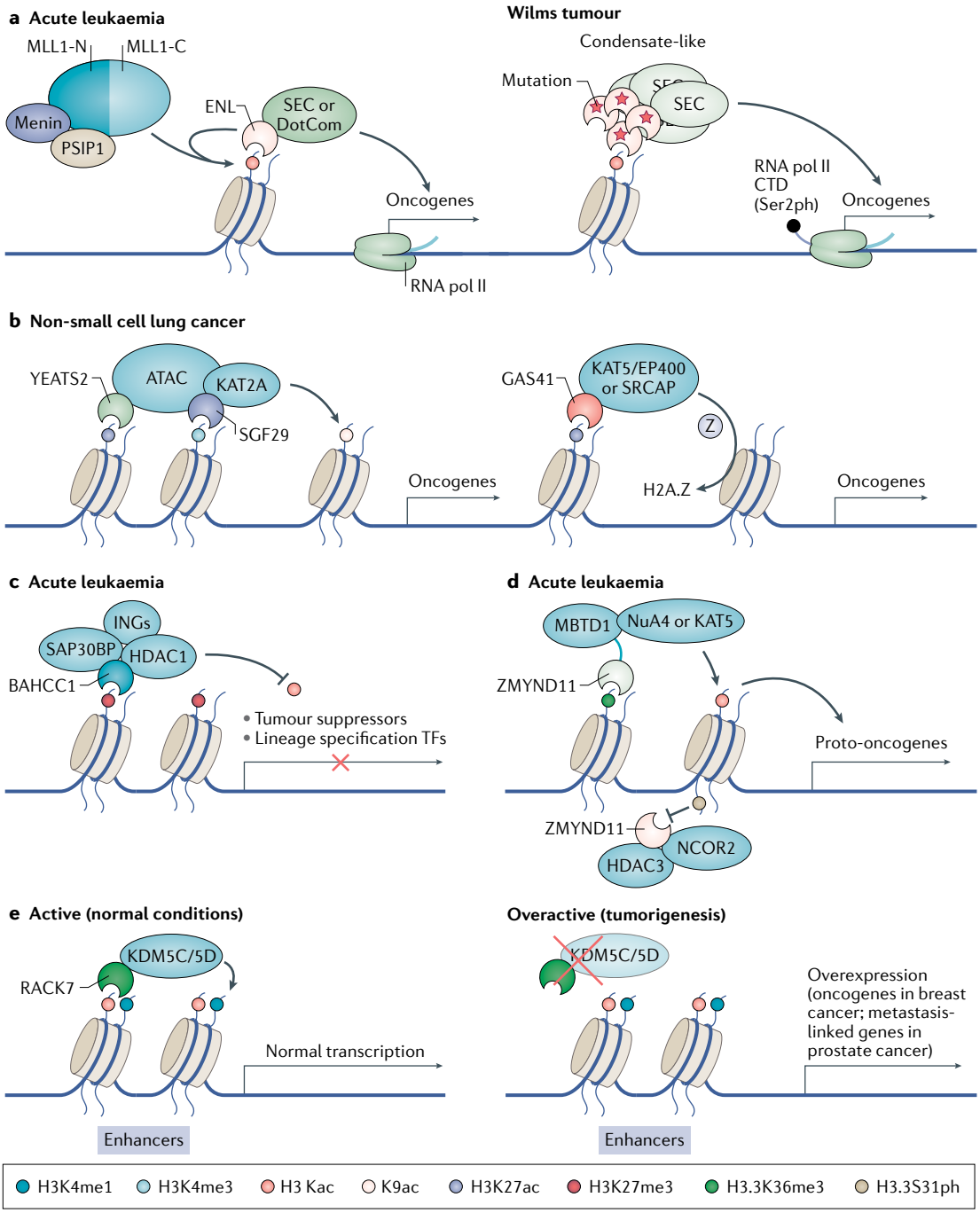
YEATS domain proteins recognize and bind histone acetylation and crotonylation. In humans, there are four YEATS domain-containing proteins — AF9, ENL, YEATS2 and GAS41 (also known as YEATS4). The YEATS domain of AF9 was initially identified as a histone acetylation reader, with a noted preference for H3K9ac[163]; likewise, a YEATS domain harboured within ENL binds to H3K27ac and H3K9ac[164,165]. Recognition of H3K27ac and H3K9ac by the YEATS modules of AF9 and ENL helps to recruit and/or stabilize transcriptional (co)activator machineries (including SEC, DOT1L, RNA polymerase II and others) onto targets, mediating active transcription[163–165] (FIG. 3a). In acute leukaemias, AF9 and ENL are frequently fused with MLL, generating an abnormal chimeric oncoprotein of MLL–AF9 or MLL–ENL, respectively, which retains capability for SEC and DOT1L recruitment. Two independent studies demonstrated that ENL, instead of AF9, is required for tumorigenicity of MLL-rearranged AML in mouse xenograft models[164,165]. In AML, the H3ac-binding-defective mutation of the ENL YEATS domain largely phenocopied ENL depletion, impaired recruitment of SEC and RNA polymerase II, and rendered AML sensitive to inhibitors of bromodomain-containing proteins and DOT1L. Combining inhibitors of YEATS domain, bromodomain and DOT1L thus provides a promising therapeutic strategy. In support of this, a peptide-based inhibitor selective for the YEATS domain of ENL was recently developed, which acts synergistically with bromodomain and DOT1L inhibitors in killing leukaemia cells[166].

Recurrent mutations of the ENL YEATS domain also exist in Wilms tumours; these mutations are characterized by small in-frame amino acid insertions or deletions that are distant from the Kac-binding pocket of the YEATS domain[167,168]. While these YEATS-mutant ENL proteins bind acetylated histones with similar affinities and also occupy similar genomic loci to wild-type ENL, they exhibit stronger self-association and enhanced binding to chromatin targets[169]. Consistently, the intrinsically disordered regions harboured within ENL were recently shown to promote multivalent phase separation of SEC, allowing rapid, robust transcriptional activation[169,170]. Thus, phase separation-like behaviour seen with the ENL YEATS mutants most likely contributes to the increased recruitment and targeting of SEC and phosphorylated RNA polymerase II onto target genes for enforcing oncogenic programmes (FIG. 3a; BOX 2). Such a GOF form of ENL enforces aberrant activation of ENL targets such as the development-associated HOX family genes, thereby impairing cell-fate regulation during development of Wilms tumour[169]. Likewise, MLL–ENL oncoproteins also boosted phase separation-like properties of SEC, suggesting a role of abnormal SEC phase separation in leukaemogenesis[170]. These examples collectively illustrate how cancer-related proteins 'interpret' and engage specific histone modification by assembling downstream coactivator complexes at chromatin targets, at least partly via phase-separated protein condensates, to induce oncogenesis.

Two other YEATS-containing proteins, YEATS2 and GAS41, were also shown to be oncogenic[171,172]. YEATS2, a subunit of histone acetyltranferase Ada-two-A-containing (ATAC) complex, is amplified in non-small cell lung cancer (NSCLC). Recognition and binding of H3K27ac by the YEATS domain of YEATS2 facilitates subsequent ATAC-mediated deposition of H3K9ac, reinforcing target gene activation[171] (FIG. 3b). Similarly, the YEATS domain contained within GAS41 binds to

Hypomorphic
Describes mutation that causes a partial loss of gene function (such as reduced enzymatic activity).

Intrinsically disordered regions
Flexible linkers or loops within a protein that form no secondary structure and often mediate phase separation.



H3K27ac and H3K14ac[172]. In NSCLC, GAS41 co-localizes with H3K27ac and H3K14ac, an event required for genome-wide deposition of histone variant H2A.Z at target promoters[172] (FIG. 3b). Disrupting the YEATS reader-mediated interaction of YEATS2 or GAS41 with histone acetyl marks slowed NSCLC growth and suppressed transformation in mouse xenograft models[171,172].

Compared with the bromodomains, YEATS domain generally has a longer and flatter binding channel, which accommodates longer and bulkier non-acetyl acylation[16] (Supplementary Fig. 1j). In vitro binding assays indeed showed histone Kcr bound most strongly to the YEATS domain[16,173–175]. Owing to a π-electron conjugation, the crotonylamide group of Kcr is planar, forming a π-π-π stacking with aromatic residues of YEATS[16,173–175] (Supplementary Fig. 1j). AF9 also co-localizes with H3K18cr, activating gene expression in macrophages[16]. H3K18cr can be induced at the de novo activated gene-regulatory elements upon lipopolysaccharide (LPS) stimulation of macrophages[176], and knocking down AF9 significantly reduced the LPS-induced gene-stimulation effect, which cannot be rescued by the YEATS mutant of AF9 (REF.[16]).

A new class of H3K27me3-specific reader: the BAH module. H3K27me3 regulates gene silencing and cell differentiation, misregulation of which is a frequent event in tumorigenesis[177]. Recently, Fan et al.[178] reported that an evolutionarily conserved bromo-adjacent

π-π-π stacking
The noncovalent interaction between aromatic rings.

◀ Fig. 3 | **Misinterpretation of histone modification in cancer. a** | The YEATS domain of ENL recognizes acetylated lysine (Kac). ENL, which interacts with the mixed lineage leukaemia 1 (MLL1) fusion oncoprotein, recruits the super elongation complex (SEC) or DOT1L complex (DotCom) into target oncogenes, maintaining a potently activated state in leukaemia cells. The ENL gain-of-function mutations facilitate self-aggregation and form phase-separated puncta. The concentrated ENL mutant proteins recruit more SEC for activation of oncogenes in Wilms tumour. **b** | The histone acetyltransferase Ada-two-A-containing (ATAC) complex contains a subunit YEATS2, which recognizes H3K27ac, and a subunit SAGA-associated factor 29 (SGF29), which recognizes H3K4me3. The catalytic subunit consisting of histone acetyltransferase KAT2A results in elevated H3K9ac and activates expression of oncogenes in non-small cell lung cancer. The YEATS domain of GAS41 recognizes H3K27ac and H3K14ac at promoter regions. GAS41 is a subunit of chromatin remodelling complexes SRCAP and TIP60–EP400. The remodelling complex SRCAP substitutes histone H2A with histone variant H2A.Z and thus activates gene expression. **c** | BAH and coiled-coil domain-containing protein 1 (BAHCC1) binds to H3K27me3-marked chromatin regions through a conserved BAH domain. BAHCC1 interacts with corepressors including histone deacetylases (HDACs) and SAP30 binding protein (SAP30BP) to silence tumour suppressor genes and lineage-specification transcription factors (TFs) in acute leukaemias. **d** | Histone modifications H3.3K36me3 and phosphorylated Ser31 on histone H3.3 (H3.3S31ph) influence chromatin localization of zinc finger MYND domain-containing protein 11 (ZMYND11). ZMYND11 specifically recognizes H3.3K36me3 at gene bodies and functions as a transcriptional corepressor by recruiting the NCOR2–HDAC3 complex. H3.3S31ph leads to the ejection of ZMYND11 from its binding sites. A ZMYND11–MBTD1 fusion protein was identified in a subset of patients with acute myeloid leukaemia. The PWWP domain of ZMYND11 binds to H3K36me3 and the fusion partner (MBTD1) recruits the nucleosome acetyltransferase of H4 (NuA4)–TIP60 histone acetyltransferase complex. Elevated histone acetylation maintains the high expression of pro-leukaemic genes in leukaemia stem cells. **e** | Under normal conditions, the tumour suppressor RACK7 recognizes the H3 tail carrying lysine acetylation and/or H3K4me1 and recruits the H3K4me3 erasers KDM5C and KDM5D onto enhancer regions. Loss of the RACK7–KDM5C/5D complex fails to demethylate H3K4me3 and results in overexpression of oncogenes (such as S100A) and metastasis-linked genes (such as *SLUG* and *VEGFA*) in breast and prostate tumour cells. CTD, C-terminal domain; RNA pol II, RNA polymerase II.

homology (BAH) module harboured within BAH and coiled-coil domain-containing protein 1 (BAHCC1), a chromatin regulator significantly overexpressed in patients with acute leukaemia, recognizes and binds to H3K27me3 and enforces silencing of Polycomb target genes (Supplementary Fig. 1k). BAHCC1 interacts with corepressors such as HDACs and SAP30 binding protein (SAP30BP), thus providing a molecular basis for Polycomb gene silencing[178]. In acute leukaemias, depletion of BAHCC1, or disruption of its BAH-mediated 'readout' of H3K27me3, caused derepression of H3K27me3-demarcated genes involved in tumour suppression and cell differentiation, which in turn suppressed tumorigenesis in mouse xenograft models of leukaemia (FIG. 3c). This study thereby unveils a novel H3K27me3-directed transduction pathway in mammalian cells that relies on a conserved BAH reader, deregulation of which contributes to oncogenesis.

PWWP domains and 'readout' of H3K36me2/3. Evidence suggests PWWP as a multivalent reader of H3K36me2/3 and nucleosomal DNA[179]. Recognition of H3K36me2/3 by PWWP-containing proteins is crucial to a range of processes including DNA methylation, transcriptional activation and elongation, pre-mRNA processing and DNA damage repair[106].

Notably, DNMT3A and related DNMT3B contain a PWWP domain involved in the binding of H3K36me2/3. In vitro and in vivo binding studies show that DNMT3B is recruited by H3K36me3, whereas DNMT3A is more preferentially recruited by H3K36me2 (REFS[118,120,180,181]). PWWP is one of the recurrently mutated domains of DNMT3A in patients with clonal haematopoiesis, haematological cancers and paraganglioma[142,181]. Misinterpretation of H3K36me2/3 owing to mutation of the DNMT3A PWWP domain was also recently reported to be responsible for microcephalic dwarfism[182]. Thus, H3K36me2/3 'misreading' mechanisms frequently underlie deregulation of DNA methylation during oncogenesis and pathogenesis.

The tumour suppressor and transcriptional corepressor zinc finger MYND domain-containing protein 11 (ZMYND11; also known as BS69) harbours a PHD–bromo–PWWP combination cassette that functions as a histone variant H3.3-specific reader of H3K36me3 (REFS[183,184]) (Supplementary Fig. 1l). Low expression of ZMYND11 is associated with poor outcome in patients with triple-negative breast cancer. Via its PHD–bromo–PWWP module, ZMYND11 interacts with H3.3K36me3 located within gene body regions and suppresses the transition of paused RNA polymerase II to transcriptional elongation, leading to downregulation of gene-expression programmes related to tumour growth[183]; recently, Armache et al.[185] further showed that phosphorylation of H3.3 at Ser31 leads to 'ejection' of ZMYND11 from chromatin during rapid stimulation and activation of genes, indicating the dynamic nature of this pathway (FIG. 3d). Interestingly, the H3.3K36me3-'reading' module of ZMYND11 was previously reported to be involved in an aberrant gene fusion termed ZMYND11–MBTD1 among a subset of patients with AML[106,186]. A recent study further demonstrated that the H3.3K36me3-'reading' activity of ZMYND11–MBTD1 is essential for recruiting and stabilizing this chimeric oncoprotein and associated HATs onto proto-oncogenes such as *Hoxa9* and *Meis1*, which then maintains the high expression of oncogenes in LSCs and induces AML development in mouse models[187] (FIG. 3d). Altogether, by engaging gene-activation-related H3K36me3, ZMYND11 impacts on tumorigenicity in various ways.

Recognition and engagement of H3K36me3 by PWWP domains is part of the DNA damage repair process. MSH6, a DNA mismatch repair protein frequently mutated in tumours such as colorectal and uterine cancer, contains a PWWP domain for binding to H3K36me3 (REF.[188]). Both H3K36me3 and the MSH6 PWWP domain were found to be essential for chromatin localization of heterodimeric MSH2–MSH6 complex[188]. In addition, interaction between PSIP1, another PWWP domain-containing protein, and H3K36me3 helps recruit the DNA endonuclease RBBP8 (also known as CtIP) to DNA damage sites[189]. Proper 'interpretation' of H3K36me3 by a set of damage repair-related PWWP domain proteins therefore provides an important safeguard mechanism for ensuring genome stability, a process frequently deregulated in cancer.

PHD finger domains recognize various histone tail PTMs. Different subclasses of PHD finger domains 'sense' the status of H3K4 PTMs, either highly methylated or unmethylated. Previously, the PHD finger of

KDM5A (also known as JARID1A or RBP2) or PHF23 was found aberrantly fused to the nuclear pore complex protein NUP98 among a subset of AMLs[190,191]. The resultant NUP98–KDM5A and NUP98–PHF23 PHD finger chimeras were found to bind H3K4me3 and were associated with stemness and expression of leukaemogenic genes such as HOX family genes and *MEIS1*, as well as the perturbed chromatin dynamics and cell differentiation[190–192]. Recent studies further showed that the NUP98–KDM5A fusion is a driver mutation present in ~10% of acute megakaryoblastic leukaemias[193,194], and a subset of these lethal paediatric cancers also harbour a similar chimera between NUP98 and the BPTF PHD finger[195], suggesting commonality between these NUP98–PHD chimeric oncoproteins and a druggable PHD finger target[191,192].

More broadly, 'misreading' of H3K4me3 by PHD finger domain proteins such as inhibitor of growth (ING) proteins 1–5, PHF23, pygopus (PYGO) and PHF20, have been shown to exert either oncogenic or tumour-suppressive effects via improper modulation of target gene expression[9,196]. Recent studies of the tumour suppressor protein kinase C-binding protein 1 (also known as RACK7 or ZMYND8) showed that its PHD finger forms a tandem cassette together with adjacent bromo and PWWP domains for recognition of a dually modified histone H3 tail, consisting of H3K4me1K14ac[197,198]. In human breast and prostate cancer models, RACK7 was found to bind gene enhancers and suppress transcription of oncogenes (such as S100A family genes) and metastasis-linked genes (such as *SLUG* and *VEGFA*) via recruitment of the H3K4me3 erasers, KDM5C and KDM5D[197,198] (FIG. 3e). Loss of RACK7 results in abnormally elevated H3K4me3 at enhancers, leading to onco-target overactivation in tumour cells and enhanced oncogenesis in tumour xenograft models[197,198]. Also, H3.3G34R, an oncohistone detected in paediatric glioblastoma (BOX 1), can create a docking site for RACK7, which then acts to suppress genes related to major histocompatibility complex, a known mediator of antitumour immunity[199]. Thus, via various misreading mechanisms, RACK7 contributes to tumorigenesis in a wide range of cancers.

The double PHD finger (DPF) domain harboured within DPF3, a BAF chromatin remodelling complex subunit, and MOZ (also known as KAT6A) or MORF (also known as KAT6B), two closely related HATs involved in AML tumorigenicity, also emerges as a combinational reader for both the N terminus and acetylation of histone H3 (REFS[162,200,201]). Additionally, the DPF domain of MOZ or DPF2, a DPF3-related BAF subunit, can bind various histone acylations, such as crotonylation[202]. Engaging of histone ligands by the DPF module is crucial for development because DPF2 mutations that abolish histone binding were found to be responsible for a neurodevelopmental disorder, Coffin–Siris syndrome[203], as well as the affected myeloid differentiation of haematopoietic stem or progenitor cells[204]. Overall, the bromo, DPF and YEATS domains provide a toolkit for cells to recognize the subtlety and unique features of various histone acylations[15–17,162,163]. The detailed interplay of histone PTM readers with the epigenomic, transcriptomic and metabolic alterations during oncogenesis warrants further investigation.

Mis-erasing of chromatin modifications

HDACs, the erasers of Kac, have long been implicated in oncogenesis, via either histone or nonhistone substrate regulation[205]. Recently, Vlaming et al.[126] reported that inactivation of HDAC1 in thymocytes results in enhanced DOT1L activity and lymphomagenesis in mice. Like the more labile Kac, histone Kme and DNA 5mC modifications can also be reversible, a process executed by enzymes or enzyme complexes that collectively have been referred to as 'erasers' (FIG. 1a). In particular, Jumonji C (Jmj-C) domain-containing proteins form a large family of histone lysine demethylases (KDMs)[206], and DNA 5mC is 'erased' by TET family proteins through successive oxidizations[3]. Both Jmj-C domain proteins and TET family proteins are Fe(II) and 2-oxoglutarate (2-OG)-dependent enzymes. Cellular metabolites and hypoxic conditions influence the Fe(II) and 2-OG level, thereby affecting the enzymatic activities of Jmj-C domain-containing and TET proteins[207].

Deregulation of Jumonji C domain causes mis-erasing of histone methylation. While non-Jmj-C proteins KDM1A (also known as LSD1) and KDM1B (also known as LSD2) are FAD-dependent monoamine oxidases catalysing demethylation of histone H3K4me1 and H3K4me2 (REF.[208]), a larger family of Jmj-C domain proteins are Fe(II) and 2-OG-dependent hydroxylases that catalyse demethylation of various histone sites and of all methylation states[206] (Supplementary Fig. 1m).

Malfunction of KDMs is a common theme among cancers[206]. Depending on cancer type and context, Jmj-C domain proteins have both oncogenic and tumour-suppressive functions. For example, while the KDM5 family proteins act as tumour suppressors in MLL-rearranged AML and clear cell renal cell carcinoma by transcriptionally repressing oncogenes[209,210], they are generally regarded as oncogenes in other tumours such as breast cancer and melanoma, in which KDM5A is frequently overexpressed[211–214]. For example, KDM5B suppresses a stimulator of interferon genes (STING)-related pathway of antitumour immunity[211] and can additionally promote drug resistance in multiple cancer types such as melanoma, breast tumour and lung cancer[212–214]. These oncogenic effects of KDM5B can be reversed by inhibitors that target its demethylating function, demonstrating an attractive means of targeting mis-erased H3K4me3 or H3K4me2 PTMs that are required for tumorigenicity[213].

Different erasers can mediate opposing effects on tumour growth, even when acting on the same histone mark. For instance, both KDM6A and KDM6B (also known as JMJD3) are H3K27me3 and H3K27me2 erasers. In murine models of T-ALL, KDM6B was reported to activate the NOTCH1-related axis by eliminating oncogene-associated H3K27me3, thus promoting T-ALL oncogenesis; meanwhile, KDM6A activated tumour suppressor genes thereby inhibiting T-ALL development[215] (FIG. 4a). Furthermore, LOF mutations in

Oncometabolite
A metabolite that is significantly elevated in quantity in tumours.

KDM6A are frequently present in various solid cancers, further supporting a tumour-suppressive role[85].

The eraser activity of the Jmj-C domain requires 2-OG, which can be competitively inhibited by its analogue 2-hydroxyglutarate (2-HG). Normally, 2-OG is generated from glutamine in cells. However, the core region of solid tumours features glutamine deficiency and a decreased 2-OG level, which leads to elevated H3K9me3 and H3K27me3 (REFS[216,217]). Low-glutamine-induced histone hypermethylation, notably H3K27me3, induced cancer cell dedifferentiation and drug resistance in xenografted melanoma models, impacting on both tumour heterogeneity and therapeutic response[216]. Moreover, the isocitrate dehydrogenase (IDH) metabolic enzymes convert isocitrate into 2-OG[218]. IDH1 is cytosolic while IDH2 is a mitochondrial protein[218]. *IDH1* and *IDH2* mutations are somatic, predominantly heterozygous and mutually exclusive[219]. Tumours carrying a GOF mutation of *IDH1* or *IDH2* produce an astonishingly high level of D-2-HG, a so-called oncometabolite that competes with 2-OG[220,221]. 2-HG is a chiral metabolite that has D-(*R*)- and L-(*S*)-enantiomeric conformations. IDH mutants specifically generate D-2-HG while L-2-HG can be generated under hypoxic conditions[222]. Both D-2-HG and L-2-HG inhibit the erasing function of Jmj-C domain proteins and impair histone demethylation[221–224].

TET inactivation causes mis-erasing of DNA cytosine methylation. 5mC in DNA (Supplementary Fig. 1a) is erased through successive oxidizations by TET1, TET2 or TET3 (REFS[225–227]). Malfunctions of TET family proteins are responsible for a wide range of haematological cancers and certain solid tumours[228]. *TET2* mutations, as detected in myeloid cancers, are both truncation mutations and missense substitutions centred within the region encoding the catalytic domain, all of which impair the 5mC erasing activity of TET2 (REF.[229]) (Supplementary Fig. 1n).

TET family proteins are regulated by various proteins and metabolites. For example, a WNT pathway protein, CXXC-type zinc finger protein 4 (CXXC4, also known as IDAX), downregulates TET2 by caspase activation[230]. Like Jmj-C domain proteins, activity of TET family proteins also relies on 2-OG as a cofactor, and hence they are sensitive to levels of the oncometabolite 2-HG[221,231]. *IDH1*, *IDH2* and *TET2* mutations in cancers are mutually exclusive[231]. *IDH1* and *IDH2* mutations inhibit TET2 function and result in DNA hypermethylation in cancers[231]. Molecular oxygen, ascorbic acid and reduced Fe(II) are additional cofactors of TET family proteins. Consequently, tumour-associated hypoxia can reduce TET activity, causing DNA hypermethylation at promoters of tumour suppressor genes[232]. On the other hand, vitamin C, an antioxidant regulating Fe(II) reduction, potentiates TET-mediated demethylation. It has been shown that vitamin C levels can influence leukaemogenesis by regulating TET family proteins[233–235]. As haploinsufficiency of TET family proteins is a frequent event in haematological cancer, treatment with high-dose vitamin C may restore TET2 deficiency and represents a possible therapeutic strategy, a topic under active investigation[235].

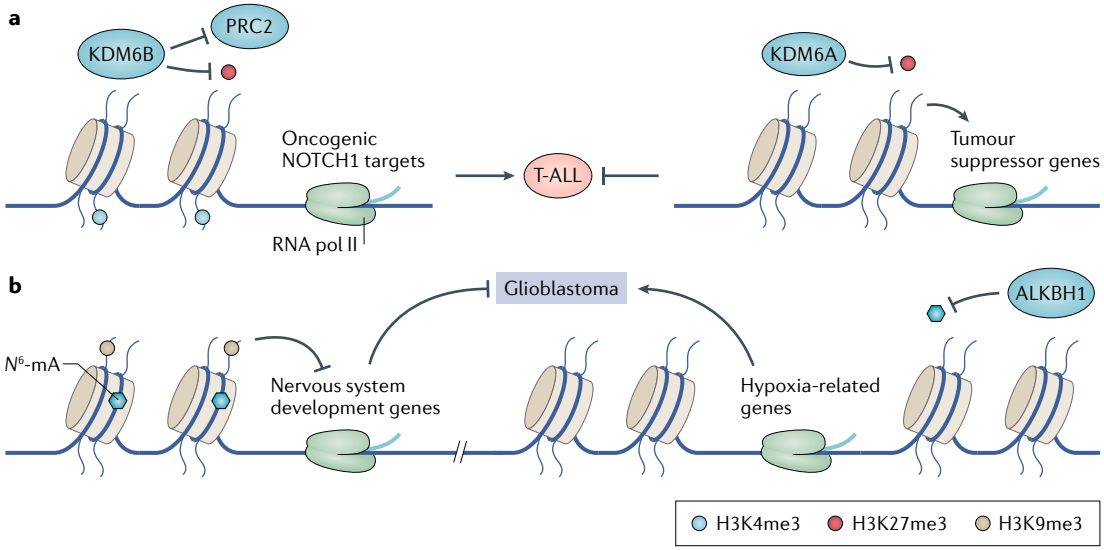


Fig. 4 | **Mis-erasing of chromatin modification is critically involved in cancer initiation and progression. a** | In T cell acute lymphoblastic leukaemia (T-ALL), the expression level of KDM6B increases while the KDM6A level decreases. Both KDM6A and KDM6B are erasers of H3K27me3. KDM6B binds to oncogenic NOTCH1 target genes, catalyses the demethylation of H3K27me3 and antagonizes the Polycomb repressive complex 2 (PRC2), an H3K27me3 writer. Decreased H3K27me3 and increased H3K4me3 facilitate the expression of oncogenic genes. By contrast, KDM6A binds to tumour suppressor genes and facilitates their expression. KDM6A thus functions as tumour suppressor in T-ALL. **b** | In glioblastoma stem cells, DNA adenine methylation (N^6-mA) coexists with H3K9me3, suppressing the neuronal differentiation-related gene-expression programme. Depletion of the nucleic acid dioxygenase ALKBH1 in glioblastoma facilitates silencing of oncogenic genes and thus decreases glioblastoma stem cell proliferation. The genomic deposition of N^6-mA appears to be context dependent and merits further study. RNA pol II, RNA polymerase II.

Dioxygenase
Oxidoreductase enzyme that incorporates both atoms of O_2 into the substrate.

R-loops
Three-stranded nucleic acid structures formed by one DNA–RNA duplex and one associated non-template single-strand DNA.

Altogether, deregulation of TET family proteins, the m5C erasers, exerts a plethora of context-dependent effects on cancer evolution and progression, stem cell ageing and clonal haematopoiesis, immunity and cellular responses to environmental cues.

ALKBH family demethylases erase DNA adenine methylation. The abundance of DNA adenine methylation (N^6-mA) (Supplementary Fig. 1a) in normal mammalian cells is very low, typically below 20 parts per million[236–238]. However, a study reported that the N^6-mA level in glioblastoma stem cells from patients with cancer can be elevated by more than 100-fold, compared with normal astrocytes; this correlated with levels of H3K9me3 and functioned as a repressive mark[239]. Increased levels of N^6-mA were also observed in other central nervous system cancers, such as diffuse intrinsic pontine glioma, meningioma and medulloblastoma[239].

The Fe(II)- and 2-OG-dependent nucleic acid dioxygenase ALKBH1 is an N^6-mA eraser[236,239,240]. In patient-derived xenograft models of glioblastoma, knockdown of ALKBH1 increased the level of N^6-mA and induced transcriptional silencing of hypoxia-related oncogenes through decreased chromatin accessibility, thereby inhibiting glioblastoma growth[239] (FIG. 4b). Under hypoxic stress, levels of N^6-mA in mitochondrial DNA are also significantly elevated, indicating its relationship with cell stress[241]. ALKBH1 favours a 'bubble' DNA structure instead of B-form duplex[242,243] (Supplementary Fig. 1o), consistent with the discovery that N^6-mA is more enriched at regions with stress-induced DNA double helix destabilization and/or R-loops[244–246]. Other potential regulators of DNA N^6-mA modification were recently proposed, such as the methyltransferase METTL4 (on mitochondrial DNA[241]) and the METTL3–METTL14 complex (on single-strand and unpaired DNA[247]), the DNA-binding protein SATB1 (binding of which is repelled by N^6-mA[244]) and YTH domain-containing protein 1 (YTHDC1, which binds to N^6-mA on single-strand DNA[248]). These molecular players are likely to regulate DNA and/or RNA, in a context-dependent manner. However, additional verification and functional characterizations are warranted[238,249]. In particular, a reliable high-resolution sequencing method needs to be developed for evaluating the function of N^6-mA modification in cancer.

Future directions

Chromatin writers, readers and erasers are promising targets for pharmacological manipulation. Certain first-generation epigenetic drugs targeting DNMTs and HDACs have been approved for clinical use, for example, in treatment of T cell lymphoma and multiple myeloma. The next-generation small molecules targeting various chromatin modulators are being developed with improved selectivity and potency, some of which are currently under clinical evalution[250]. Chromatin modulator targets that proved to be druggable include writers (such as EZH2, DOT1L and EP300), readers (such as bromodomain-containing proteins) and erasers (such as KDM5 and HDACs). Aside from those directed against epigenetic modulators per se, inhibitors of cancer-related metabolic enzymes, such as GOF IDH1 or IDH2 mutant proteins, show promising results as well, reversing their pro-tumour epigenetic effects[250]. For detailed progress in this area, we recommend recent reviews[134,250].

Chromatin modulators are also suitable for new drug development strategies such as heterobifunctional proteolysis targeting chimeras (PROTACs)[251], which have several advantages. First, instead of targeting one aspect of multifunctional chromatin modulators, PROTACs bring about target protein degradation, thus temporally eliminating all functions of targets to exert strong antitumour effects. Second, PROTACs can be more potent; owing to their catalytic mechanism of action, PROTACs can be reused for repeated cycles of target depletion, potentially reducing the need for high residence time and continuous drug exposure relative to small-molecule inhibitors that typically rely on receptor occupancy pharmacology. Thirdly, PROTACs can potentially improve drug specificity by introducing more interactions between the PROTAC, the target protein and the E3-ligase ternary complex[252]. PROTACs may therefore have the potential to improve specificity and efficacy of the existing inhibitors available for targeting chromatin regulators, may effectively suppress target chromatin-regulatory oncoproteins that are often multifunctional in cancer, and may address drug resistance[253]. In support of this, PROTACs targeting BRD4 (REF.[254]), HDACs[255] and EZH2 (REF.[256]) are being developed and show promising effects in vitro and in vivo.

Lastly, epigenetic variations contribute to tumour heterogeneity[36–38]. With recent advances in single cell-based chromatin modification profiling technologies[257,258], we anticipate more comprehensive mapping of cancer epigenomes, at both the spatial and temporal levels (4D) during the dynamic course of cancer evolution[36]. Tumour cell adaptation and therapeutic resistance frequently occur; therefore, future studies should explore strategies to address this, such as epigenetic synthetic lethality and combination therapy, for (epi)targeting of human cancers. For example, treatment with a bromodomain inhibitor leads to accumulation of DNA damage in tumours and thus a high demand for DNA damage repair machinery, which renders tumours hypersensitive to PARP inhibitors[259,260]. Likewise, combining epigenetic therapies with immunotherapies represents another attractive means of enhancing treatment success[261]. Further dissection of potential crosstalk between epigenetic players and other cancer-related pathways will continue to have an impact on cancer therapeutics and medicine.

Conclusions

The molecular understanding of chromatin deregulation, one of the central mechanisms underlying oncogenesis, together with development of potent and specific pharmacological agents, will aid in the development of effective treatments for human cancers. We look forward to further advances along these lines in years to come.

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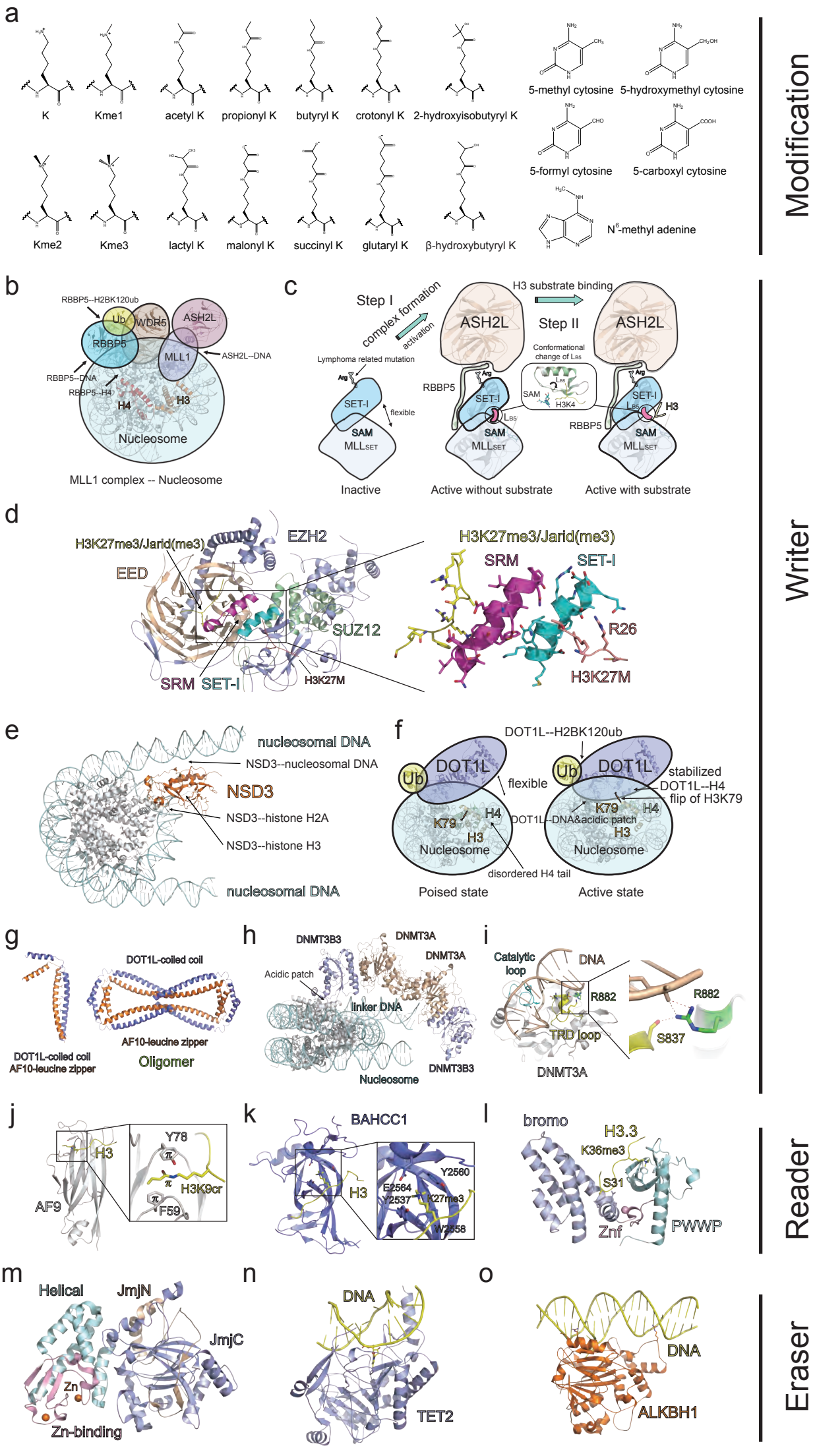
a
K
Kme1
acetyl K
propionyl K
butyryl K
crotonyl K
2-hydroxyisobutyryl K
5-methyl cytosine
5-hydroxymethyl cytosine
Kme2
Kme3
lactyl K
malonyl K
succinyl K
glutaryl K
β-hydroxybutyryl K
5-formyl cytosine
5-carboxyl cytosine
N6-methyl adenine
Modification
b
RBBP5--H2BK120ub
Ub
WDR5
ASH2L
RBBP5
MLL1
ASH2L--DNA
RBBP5--DNA
RBBP5--H4
H4
H3
Nucleosome
MLL1 complex -- Nucleosome
c
Step I
complex formation
activation
Lymphoma related mutation
Arg
SET-I
flexible
SAM
MLLSET
Inactive
H3 substrate binding
Step II
ASH2L
RBBP5
Conformational change of LB5
SAM
H3K4
Active without substrate
Active with substrate
H3
d
H3K27me3/Jarid(me3)
EZH2
EED
SUZ12
SRM
SET-I
H3K27M
R26
e
nucleosomal DNA
NSD3--nucleosomal DNA
NSD3
NSD3--histone H2A
NSD3--histone H3
f
DOT1L--H2BK120ub
DOT1L
Ub
flexible
stabilized
DOT1L--H4
flip of H3K79
K79
H4
H3
Nucleosome
DOT1L--DNA&acidic patch
disordered H4 tail
Poised state
Active state
Writer
g
DOT1L-coiled coil
AF10-leucine zipper
Oligomer
h
DNMT3B3
DNMT3A
Acidic patch
linker DNA
Nucleosome
i
Catalytic loop
DNA
R882
TRD loop
S837
DNMT3A
j
H3
Y78
H3K9cr
F59
AF9
k
BAHCC1
H3
Y2560
E2564
Y2537
K27me3
W2558
l
bromo
H3.3
K36me3
S31
Znf
PWWP
Reader
m
Helical
JmjN
JmjC
Zn
Zn-binding
n
DNA
TET2
o
DNA
ALKBH1
Eraser