MedScience 2026, 20(1): 3−22
https://doi.org/10.1007/s11684-026-1209-z

REVIEW

Mono-ubiquitination of histone H2A lysine 119 (H2AK119Ub): its multifaceted role in biology and implication in diseases

Damu Wu[1], Haiqing Zhong[1], Ling Cai[2,3], Gang Greg Wang (✉)[1,2,3]

[1]Department of Pharmacology and Cancer Biology, Duke University School of Medicine, Durham, NC 27710, USA; [2]Department of Pathology, Duke University School of Medicine, Durham, NC 27710, USA; [3]Duke Cancer Institute, Duke University School of Medicine, Durham, NC 27710, USA

Abstract **Mono-ubiquitination of histone H2A at lysine 119 (H2AK119Ub) is deposited by the Polycomb repressive complex 1 (PRC1) and represents an abundant post-translational modification (PTM) of histones. H2AK119Ub is crucially involved in the regulation of a wide range of biological processes, including organization of the genome into distinct functional domains, gene silencing, and the maintenance of cell identities during development, among others. Biochemically, the deposition and removal of H2AK119Ub are tightly controlled in cells owing to a dynamic balance between the specific "writers" (i.e., PRC1) and "erasers" (i.e., deubiquitinases (DUBs) such as BAP1 and USP16). Furthermore, the increasing evidence establishes a notion that H2AK119Ub serves as a signal for recruiting specific "readers" (such as JARID2, DNMT3A, RYBP, SSX, and RSF1), which elicit the critical downstream effects such as modulating gene transcription, maintaining genome integrity, and shaping cell identity. This H2AK119Ub-based signaling is often perturbed in human diseases, pointing to a connection between its dysregulation and pathological development. This review is aimed at providing a timely, in-depth analysis of the molecular machinery governing H2AK119Ub, its interactions with other chromatin factors, and its causal role in the onset and progression of diseases, notably cancer.**

Keywords histone; ubiquitination; H2AK119Ub; epigenetics; gene regulation; transcription; Polycomb; cancer; ubiquitin-interacting motif (UIM); ubiquitin-dependent recruitment region (UDR); DNMT3A; methyltransferase

Introduction

Histone post-translational modifications (PTMs), such as acetylation, phosphorylation, ubiquitination and methylation, are critical regulators of chromatin dynamics and the epigenetic states of cells [1]. Ubiquitination of the histone H2A represents an abundant type of histone PTMs in the mammals, present on roughly 10% of all H2A molecules. Ubiquitination occurs at multiple sites of H2A, such as its lysine residues 13, 15, 119, and 129, and these modifications have been reported to mediate distinct biological processes. For example, H2AK13/15Ub, catalyzed by the RNF8–RNF168 cascade, plays a critical role in the DNA damage response by recruiting 53BP1 and coordinating assembly of repair factors [2–5]. In contrast, H2AK129Ub contributes to chromatin compaction and genome stability through PRC1-independent mechanisms [6–8]. The most prominent and extensively characterized ubiquitination of H2A is the one at the residue K119, H2AK119Ub, which this review article is focused on. Catalyzed by Polycomb repressive complex 1 (PRC1), H2AK119Ub is essential for the establishment and maintenance of gene silencing, as well as determination of cellular states and fates, during organismal development; when mis-regulated, is critically linked to pathogenesis such as cancer [9,10]. Accumulating evidence supports that H2AK119Ub functions as a platform for recruiting the effector proteins, or "readers," which can modulate the gene-expression programs and the epigenetic states under various biological contexts. Traditionally, H2AK119Ub has been viewed as a histone PTM downstream of PRC2 and the PRC2-deposited trimethylation of histone H3 lysine 27 (H3K27me3); however, studies now show that it also serves as an instructive signal that precedes and facilitates the PRC2 recruitment, leading to the establishment of H3K27me3 [11–13]. Indeed, the identification of the PRC1 variant subcomplex termed vPRC1—which lacks the canonical chromobox (CBX) subunit but contains

Received September 2, 2025; accepted December 16, 2025
Correspondence: Gang Greg Wang, greg.wang@duke.edu

RING1 and YY1 binding protein (RYBP) or YY1-associated factor 2 (YAF2) instead—has redefined the Polycomb complexes-mediated regulatory axes, showing that the deposition of H2AK119Ub can occur independently of H3K27me3 and is essential for initiating the *de novo* establishment of Polycomb domains (positive for H2AK119Ub and H3K27me3; Fig. 1), particularly at the developmental gene promoters [11–13].

Recently, several H2AK119Ub "readers" (Table 1)—notably, Jumonji and AT-rich interaction domain-containing 2 (JARID2), DNA methyltransferase 3A isoform 1 (DNMT3A1), RYBP, and remodeling and spacing factor 1 (RSF1)—have been identified, greatly expanding the current understanding of how this histone PTM is interpreted and relayed into a variety of downstream events in the cell. In general, these "readers" recognize H2AK119Ub in a nucleosomal context through distinct structural modules, which include the ubiquitin-interacting motif (UIM) of JARID2 [14], the ubiquitin-dependent recruitment region (UDR) of DNMT3A1 [15–17], the Npl4 zinc finger (NZF) domain of RYBP [18,19], and the ubiquitin-associated binding (UAB) domain of RSF1 [20]. Structural studies of these factors and the H2AK119Ub-containing nucleosome further demonstrated their interactions to be highly specific, with "readers" acting as the scaffold to recruit the functionally distinct chromatin-modifying and gene-regulatory complexes. For instance, JARID2 and DNMT3A1, two of the H2AK119Ub "readers," act to reinforce transcriptional silencing at the target genes [21,22]. Notably, the H2AK119Ub "readers" are not exclusively repressors. RSF1, for example, has been shown to bind the H2AK119Ub-marked nucleosomes and facilitate the PRC1 displacement from chromatin, promoting transcriptional activation at select genomic loci [20]. Therefore, the dual roles for H2AK119Ub were reported to either stabilize a gene-repressive state or permit reactivation, depending on the "reader" identity and cellular contexts.

Dysregulation of H2AK119Ub signaling is implicated in a spectrum of human diseases, pointing to the importance of this pathway in biology and medicine. It is conceivable that H2AK119Ub malfunction, due to inherited mutation or altered expression of H2AK119Ub "readers," can cause inappropriate activation or repression of developmentally crucial genes and the increase of cellular plasticity, thereby contributing to malignant transformation and/or congenital disorders. For

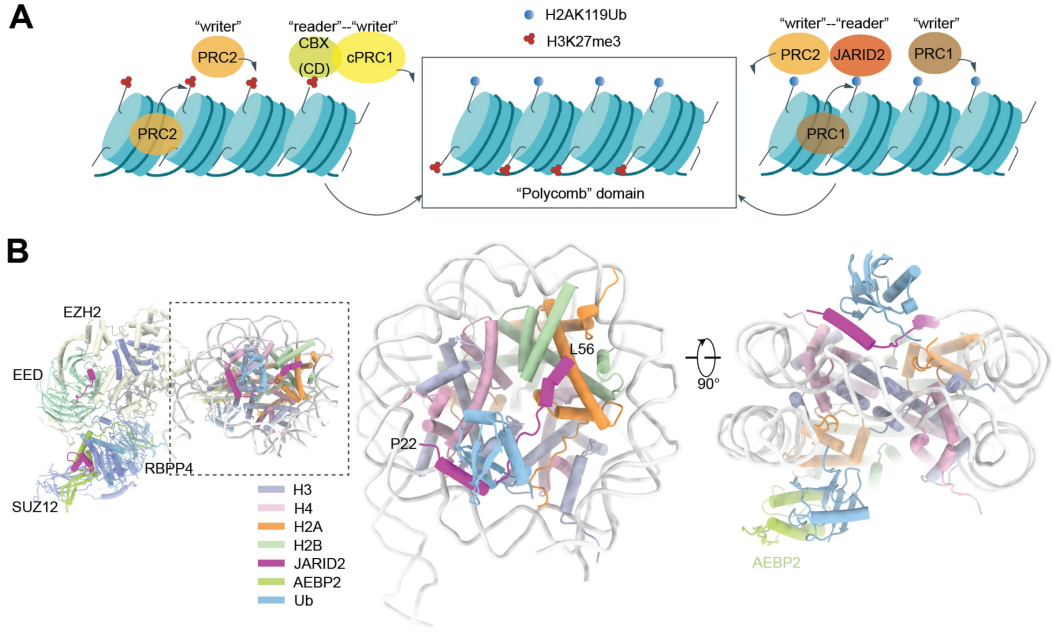

Fig. 1 Synergistic actions of PRC1 and PRC2 lead to stable epigenetic repression. (A) Schematic illustration of the crosstalk and feedback regulation among PRC1, PRC2, and "readers" of their deposited histone PTMs (i.e., H3K27me3 and H2AK119Ub). Left panel: H3K27me3, which is deposited by PRC2 (the H3K27me3 "writer"), is directly bound by the chromodomain (CD) harbored in the CBX protein (the H3K27me3 "reader"), which recruits the canonical PRC1 (cPRC1) complex (the H2AK119Ub "writer"). Right panel: PRC1 (the H2AK119Ub "writer") catalyzes H2AK119Ub, which facilitates the PRC2 recruitment via JARID2 (the H2AK119Ub "reader") to enhance the H3K27me3 deposition. Middle panel: a bidirectional communication, enforced at least by a PRC1-H2AK119Ub-JARID2:PRC2-H3K27me3 axis and a PRC2-H3K27me3-CBX:PRC1-H2AK119Ub axis, establishes the so-called "Polycomb domain," a more stable repressive chromatin state. (B) Structural model of the PRC2–AEBP2–JARID2 complex bound to an H2AK119Ub-modified nucleosome (PDB: 6WKR). JARID2 directly engages the ubiquitin moiety via its UIM, anchoring the associated PRC2 to the nucleosome and stimulating its catalytic activity. Right panels are zoomed-in views of the boxed part shown in the left panel. Individual subunits of the complex and nucleosomal components are color-coded and labeled as indicated.

Table 1 Summary of H2AK119Ub readers

Protein	Recognition domain/motif	Principal biological function	Disease/pathological association
JARID2	UIM (ubiquitin-interacting motif)	Links PRC1-deposited H2AK119Ub to PRC2.2-mediated H3K27me3 deposition; maintains Polycomb repression during development	Overexpression in solid tumors (e.g., the lung, colon, breast, etc.) promotes oncogenesis; loss in myeloid neoplasms impairs PRC2 recruitment and promotes leukemogenesis
DNMT3A1	UDR (ubiquitin-dependent recruitment region)	Couples the Polycomb-dependent H2AK119Ub marking with DNA methylation	DNMT3A1 PWWP mutations in cancers release the UDR-based reading of H2AK119Ub and leads to aberrant DNA hypermethylation at the Polycomb-targeted genomic sites
RYBP	NZF (Npl4 Zinc Finger)	Engages H2AK119Ub and stabilizes vPRC1 on chromatin	Dysregulated in several cancers; RYBP loss linked to enhanced tumor growth and poor prognosis
SS18::SSX or SSX	C-terminal repression domain	SS18::SSX retargets the BAF complex and perturbs the Polycomb–BAF balance, driving aberrant transcription	SS18::SSX, generated by the t(X;18)(p11.2;q11.2) chromosomal translocation, is the hallmark mutation and oncogenic driver of synovial sarcoma
ZRF1	UBD (ubiquitin binding domain)	Displaces PRC1 to allow target gene reactivation during differentiation	Dysregulated ZRF1 impairs differentiation and is implicated in cancer and neurodevelopmental disorders
RSF1	UAB (ubiquitin-associated) domain	Facilitates chromatin remodeling at Polycomb target sites and DNA damage loci	RSF1 amplification in ovarian and breast cancers; contributes to genomic instability

example, the overexpression of a key H2AK119Ub deubiquitinase (DUB), USP16, in a Ts65Dn mouse model of Down's syndrome resulted in the reduced self-renewal of hematopoietic stem cells and impaired expansion of neural progenitors, concurrent with aberrant erasure of H2AK119Ub [23]. On the other hand, USP16 deletion in murine bone marrow caused the accumulation of H2AK119Ub, impairing appropriate commitment of hematopoietic cell lineages [24]. Furthermore, the germline mutation of BAP1, another key regulator of H2AK119Ub, defines a syndrome predisposed to cancer such as uveal melanoma, mesothelioma, and cutaneous melanoma [25]. Likewise, aberrant expression of RYBP or JARID2 was reported to alter the crosstalk between PRC1 and PRC2, leading to misexpression of developmental genes and promotion of tumor progression in lung, breast, and myeloid cancers [14,26,27].

In this review, we summarize the emerging insights into the cellular machineries involved in the sensing and readout of H2AK119Ub, as well as the underlying molecular mechanisms and biological functions during various biological processes. We particularly focus on how the H2AK119Ub is interpreted under different cellular contexts, the structural principles of such recognition, and the implications of H2AK119Ub dysregulation in human diseases.

JARID2 functions as a "reader" of H2AK119Ub, establishing Polycomb domains across the genome

Initially, JARID2 was identified in 1995 by Takeuchi and colleagues through a genetic screen in searching for the regulators of mouse embryogenesis [28]. Mice deficient in JARID2 displayed cardiac malformations, such as aberrant heart morphogenesis and ventricular septal defects, highlighting its essential role in development [29]. Although JARID2 contains a JmjC domain, a structural motif typically associated with demethylase activity, subsequent studies demonstrated that it lacks catalytic activity due to the absence of conserved residues required for binding iron and α-ketoglutarate, the two cofactors of demethylase [30,31]. Despite a lack of catalytic function, JARID2 has been reported to act as a transcriptional corepressor and emerged as a key non-enzymatic regulator of chromatin dynamics, especially at the repressive genomic regions [32,33]. Proteomic studies using PRC2 as the bait revealed that JARID2 physically associates with the core PRC2 complex; together with AEBP2, JARID2 was identified as a defining component of a PRC2 complex variant termed PRC2.2 [30,34,35]. Terminology and definition of different subcomplexes for PRC2 and PRC1 have been covered in previous reviews [36,37] and therefore will not be explained here. JARID2 was shown to modulate the chromatin binding and histone methyltransferase activity of PRC2.2, thereby maintaining the Polycomb-mediated transcriptional repression [37–39].

While the above studies established JARID2 as a PRC2-regulatory factor, JARID2 has recently emerged as a functional bridge between the two major Polycomb complexes, PRC1 and PRC2, through its ability to recognize and bind H2AK119Ub directly. This discovery marked a significant advancement in the current understanding of the crosstalk between PRC1 and PRC2. In 2014, Kalb and colleagues identified JARID2 as a direct interactor of H2AK119Ub using quantitative proteomic approaches [40]. By incubating either unmodified or H2AK119Ub-modified nucleosomes with nuclear extracts from mouse embryonic stem cells

(mESCs), they discovered that JARID2 preferentially binds the H2AK119Ub-marked nucleosomes [40]. This finding unveiled a functional connection between the PRC1-deposited H2AK119Ub and PRC2 recruitment, leading to subsequent deposition of H3K27me3 (Fig. 1A, right panel). In parallel, the chromodomain (CD) of CBX family proteins within the canonical PRC1 (cPRC1) complex specifically recognizes and binds H3K27me3 to deposit H2AK119Ub, thereby reinforcing gene repression through a feedforward regulatory loop (Fig. 1A, left panel). As mentioned above, JARID2 not only facilitates the chromatin occupancy of PRC2 at H2AK119Ub-enriched regions but also enhances its histone methyltransferase activity, promoting H3K27me3 deposition at the Polycomb-targeted genomic regions. Such a dual role of JARID2 positions it to be a critical integrator of the PRC1 and PRC2 functions.

Cooper *et al*. subsequently investigated the molecular basis for JARID2-mediated H2AK119Ub recognition, identifying a UIM located within the N-terminal amino acids 24–40 of JARID2 [14]. A recent cryo-EM structure of the JARID2–AEBP2–PRC2 bound to the H2AK119Ub-modified nucleosomes has further revealed a multivalent "read-and-recruit" mechanism [21] (Fig. 1B). The UIM of JARID2 adopts an L-shaped conformation that enables multivalent interactions with the H2AK119Ub-harboring nucleosome (Fig. 1B, middle panel). Structurally, an α-helix region of the UIM establishes extensive contacts with both ubiquitin and nucleosomal DNA, anchoring the complex onto nucleosomes with high affinity. Concurrently, a C-terminal positively charged segment of the UIM establishes the electrostatic interaction with the H2A–H2B acidic patch, further stabilizing the nucleosome binding. On the opposite side of the nucleosome, Adipocyte Enhancer Binding Protein 2 (AEBP2), a zinc finger protein, contributes to the binding specificity by engaging ubiquitin through two of its three C2H2 zinc finger motifs (Fig. 1B, right panel). This multivalent interaction interface formed by JARID2 and AEBP2 greatly enhances both the affinity and specificity of binding by the PRC2.2 complex to the H2AK119Ub-marked nucleosome. Functionally, this interaction is critical for the PRC2 recruitment and H3K27me3 deposition at Polycomb-targeted genomic loci. Indeed, loss of JARID2 leads to the diminished PRC2 binding and the globally reduced H3K27me3, placing JARID2 to be a player that acts upstream of the H3K27me3 "writers" [14,34,35,40]. In addition to being a regulator of developmental genes, JARID2 also plays a central role during the X chromosome inactivation (XCI). During early embryogenesis, Xist RNA triggers the PRC1-mediated deposition of H2AK119Ub across the inactive X chromosome. In this process, H2AK119Ub is then recognized by JARID2, which facilitates the recruitment of PRC2 and spreading of H3K27me3, establishing a transcriptionally repressive chromatin environment during XCI [14,39,41,42].

JARID2 dysregulation has been linked to diseases, most notably neurodevelopmental disorders and cancers. The mutation or altered expression of JARID2 was associated with syndromic intellectual disability and neurodevelopmental disorder [43–46]. In the context of cancers, JARID2 shows complex context-dependent roles. On one hand, JARID2 overexpression was positively correlated with enhancement of the PRC2 activity and suppression of tumor suppressor genes (TSGs), contributing to the genesis of lung cancer, colon cancer, and breast cancer [26,47]. Conversely, the loss of JARID2 in myeloid neoplasms was found to be associated with impairment of the PRC2 recruitment and failure to silence the developmental genes, contributing to leukemic transformation through the enhanced progenitor self-renewal [27]. These findings highlight JARID2 as a molecular rheostat that fine-tunes PRC2 activity, functioning as either a TSG or an oncogene depending on cellular and developmental contexts.

Together, JARID2 acts as a central epigenetic integrator that links the repressive H2AK119Ub mark catalyzed by PRC1 to the methylation activity of PRC2 (Table 1). Alongside a parallel signaling involving the CBX-directed reading of H3K27me3, these findings establish a "two-way" communication that reinforces the Polycomb silencing (Fig. 1A). Depending on the cellular contexts, JARID2's regulatory roles have been established in the epigenetic gene repression, developmental fidelity, and oncogenesis.

DNMT3A1 recognizes H2AK119Ub, thereby connecting the Polycomb-based gene repression with the *de novo* DNA methylation

Three DNA methyltransferases—DNMT1, DNMT3A, and DNMT3B—mediate cytosine methylation in mammals. DNMT1 primarily functions as the maintenance methyltransferase, faithfully copying the existing methylation patterns onto newly synthesized DNA strands by targeting the hemi-methylated sites during DNA replication [48]. In parallel, DNMT3A and DNMT3B act as *de novo* methyltransferases, establishing the CpG methylation patterns during embryonic development and cellular differentiation [49]. Despite sharing considerable sequence identity, DNMT3A and DNMT3B are not functionally redundant [50,51]. DNMT3A has two predominant isoforms, a long isoform 1 (DNMT3A1) and a shorter isoform 2 (DNMT3A2), with the latter generated through alternative promoter usage and lacking the 223 N-terminal amino acids present in DNMT3A1 [52,53] (Fig. 2A). Despite displaying the

comparable methyltransferase activity *in vitro* [53], DNMT3A1 and DNMT3A2 show distinct expression patterns across the cellular types and chromatin association across the genome. DNMT3A2, predominantly expressed in ESCs and germline cells, is preferentially localized to the euchromatic regions [52–56]. In contrast, DNMT3A1 is more broadly expressed across various somatic tissues and demonstrates the enrichment at heterochromatic domains [57]. Isoform-specific distribution in the genome, accompanied by differential interaction with chromatin-associated regulators, establishes the distinct regulatory role for DNMT3A1 and DNMT3A2 in shaping the landscape of DNA methylation.

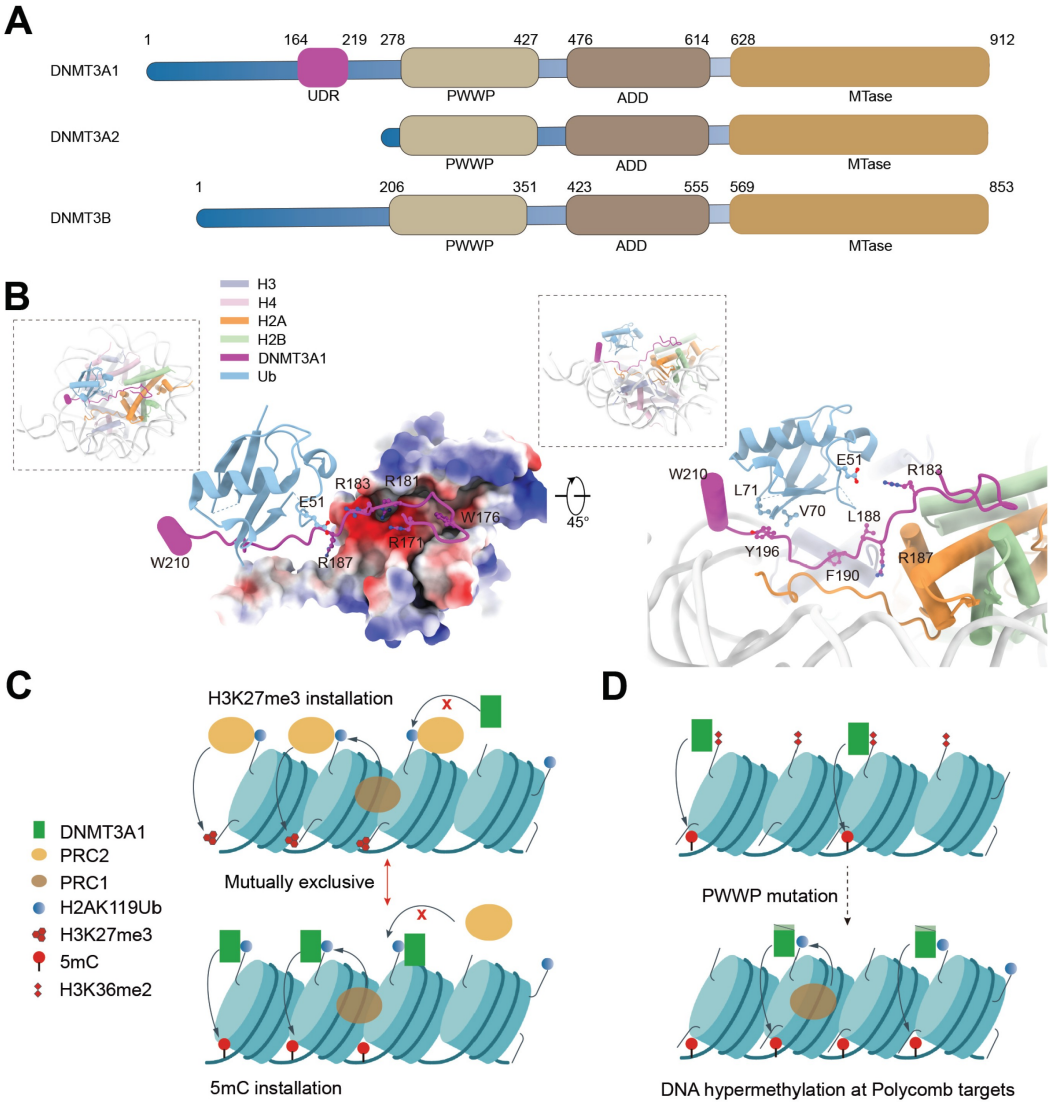

Fig. 2 The recognition of H2AK119Ub by DNMT3A1 for DNA methylation. (A) Domain architecture of DNMT3A1, DNMT3A2 and DNMT3B1. DNMT3A1 harbors a unique N-terminal ubiquitin-dependent recruitment (UDR) region that is absent in DNMT3A2 and DNMT3B1. Each domain has been colored as indicated. (B) Structural model of DNMT3A1 bound to a nucleosome carrying H2AK119Ub (PDB: 8U5H). An N-terminal region of DNMT3A1's UDR engages the H2A–H2B acidic patch, while its C-terminal region simultaneously interacts with nucleosomal DNA and the ubiquitin moiety. These multivalent interactions stabilize DNMT3A1 association with the H2AK119Ub-modified chromatin. (C) A proposed competitive model between DNMT3A1 and JARID2 for binding the H2AK119Ub-modified nucleosomes. The two "readers" utilize distinct ubiquitin-interacting motifs to recognize this histone mark, suggesting a potential regulatory competition that may influence the balance between Polycomb-mediated repression and *de novo* DNA methylation. 5mC, 5-methylcytosine. (D) A switch-binding model of DNMT3A1 carrying the PWWP-domain-defective mutation detected in cancers. In wild-type (WT) cells, the DNMT3A1 PWWP domain binds H3K36me2/3 to direct DNA methylation. In PWWP-mutated cancers, loss of H3K36me2 binding capacity of PWWP leads a UDR-based shift in DNMT3A1's chromatin occupancy toward the H2AK119Ub-rich genomic loci, resulting in aberrant DNA hypermethylation at Polycomb-regulated regions. Colors and labels of protein domains, nucleosomal elements, and interaction interfaces correspond to those depicted in the figure.

DNMT3A's genomic targeting and catalytic activity are orchestrated by a series of tandemly arranged functional modules. A key distinction between the two major isoforms lies at the N terminus—DNMT3A1 possesses an extended regulatory region absent in DNMT3A2 (Fig. 2A). Positioned downstream of this variable N terminus are a proline-tryptophan-tryptophan-proline (PWWP) domain, which recognizes and binds the histone H3 di- or tri-methylated at lysine 36 (H3K36me2/3) [58–60], and an adjacent ATRX-DNMT3-DNMT3L (ADD) domain, which recognizes and specifically binds the histone H3 non-methylated at lysine 4 (H3K4me0) [61]. The ADD domain provides a crucial autoinhibitory mechanism—in the absence of its cognate H3K4me0 ligand, it physically blocks access to DNMT3A's catalytic pocket, thus preventing spurious DNA methylation and ensuring activity is unleashed only upon the engagement with appropriate chromatin context [62,63]. At the C terminus, the catalytic methyltransferase domain (MTase) executes the enzyme's primary function—it catalyzes the transfer of a methyl group from the cofactor S-adenosylmethionine (SAM), to cytosine residues, preferentially in the CpG dinucleotides, thereby establishing *de novo* DNA methylation [62,64–66].

Recent studies have uncovered a previously unappreciated mechanism in which the regulation of DNMT3A1's enzymatic activity involves recognition of H2AK119Ub and the corresponding region termed ubiquitin-dependent recruitment (UDR; residues 164–219 of DNMT3A1), which is unique to DNMT3A1 and absent from DNMT3A2 [16,17,67]. Functional significance of the UDR emerged when DNMT3A is defective in the PWWP-mediated recognition of H3K36me2/3, leading to DNMT3A1's aberrant accumulation at genomic loci marked by H2AK119Ub [68]. Biochemical and structural studies confirmed that DNMT3A1's UDR directs high-affinity and highly specific binding to the H2AK119Ub-modified nucleosome [15–17]. These studies also reveal a multivalent binding mechanism involving at least three synergistic protein–protein interaction interfaces (Fig. 2B). First, an UDR segment spanning the residues R171 to R181 adopts a positively charged U-turn motif that docks onto the conserved H2A–H2B acidic patch, a canonical chromatin-interacting surface frequently used by Polycomb group complexes and other epigenetic regulators [69]. Within this motif, R171 and R181 directly engage the acidic patch, whereas W176 is anchored within a hydrophobic cage formed by H2A. Second, a central UDR segment immediately following the U-turn motif (L188, F190, and Y196) inserts into a hydrophobic groove formed by the C-terminal tail of H2A and an adjacent dimer interface of H3. Furthermore, the R183 residue of DNMT3A1 is oriented toward the ubiquitin moiety of H2AK119Ub and engages in an electrostatic interaction with E51 of ubiquitin. Third, the C-terminal α-helix within UDR makes additional contacts with both the conjugated ubiquitin at H2AK119 and the adjacent nucleosomal DNA. Interestingly, the N-terminal region of JARID2 also engages the H2AK119Ub-modified nucleosome through a structurally analogous interface, albeit in an opposite orientation [15]. Furthermore, DNMT3A1 and JARID2 have been shown to compete with one another for binding to H2AK119Ub-modified nucleosome *in vitro* in a mutually exclusive manner, indicative of antagonism between DNA methylation and Polycomb complex-mediated repression in cells (Fig. 2C).

These above observations point to a gene-regulatory mechanism in which H2AK119Ub serves as a hub that can potentially be engaged by distinct "readers" to elicit divergent biological effects. In support, a majority of Polycomb target sites exhibit a pattern of DNA hypomethylation during development [70]; here, JARID2 was shown to facilitate PRC2 recruitment and H3K27me3 deposition to establish the Polycomb complexes-based repression [14,17]. In contrast, the DNMT3A1 binding to H2AK119Ub promotes DNA methylation—a pattern typically associated with more stable gene silencing and heterochromatin formation. Chen *et al*. demonstrated that mutation of key residues within the DNMT3A1 UDR not only impaired the binding to H2AK119Ub-modified nucleosomes *in vitro* but also compromised the DNA methylation activity of DNMT3A1 *in vitro* and *in vivo* [15]. However, Wapenaar *et al*. reported that H2AK119Ub can increase the binding affinity of DNMT3A1 to nucleosomes *in vitro* but did not stimulate its catalytic activity, contrasting sharply with the activating role of H3K36me2/3 [17]. Furthermore, Gretarsson *et al*. conducted the DNMT3A1 re-expression in the *Dnmt3a/3b/1* triple-knockout mESCs and showed that H2AK119Ub alone is insufficient to stimulate DNMT3A1's *de novo* methylation activity in cells [16]. Together, these findings support a model in which H2AK119Ub serves as a "positioning signal," recruiting DNMT3A1 to the Polycomb-repressed genomic regions (such as bivalent promoters and unmethylated CpG islands) but leaving its catalytic activity latent in the absence of additional activating cues (such as H3K36me2/3, which is sensed by DNMT3A1's PWWP module). This working model aligns well with the genome-wide methylation profiling data, which showed that the H2AK119Ub-demarcated regions often remain hypomethylated under physiologic conditions [50,59,71], suggesting that UDR-mediated genomic targeting of DNMT3A1 primes, but does not alone trigger, the *de novo* methylation.

However, DNMT3A1 malfunction under the pathological context such as developmental disorders and cancers can lead to the perturbed activity of DNMT3A1

and the resultant reprogramming of DNA methylation patterns. Indeed, the cancer-associated mutations in DNMT3A1's PWWP domain disrupt its ability to recognize H3K36me2/3, thereby unleashing the latent chromatin-binding capacity of the UDR. As a result, DNMT3A1 becomes mistargeted to the H2AK119Ub-enriched facultative heterochromatin, particularly at the bivalent promoters and unmethylated CpG islands—regions normally protected from *de novo* methylation (Fig. 2D and Table 1). This mistargeting ultimately leads to aberrant DNA hypermethylation, a hallmark often observed in the diseased contexts [72–75]. These mechanistic insights into DNMT3A1 mislocalization have opened new avenues for therapeutic intervention. Small molecules or peptides that selectively disrupt UDR's interaction with H2AK119Ub-modified nucleosomes could prevent aberrant DNMT3A1 recruitment to Polycomb-repressed regions, thus restoring normal DNA methylation patterns in those DNMT3A1 mutant cancers or developmental syndromes. Moreover, the engineered UDR derivatives could also serve as dominant-negative inhibitors, competitively blocking endogenous DNMT3A1 from accessing the H2AK119Ub-marked targets.

RYBP functions as a "reader" and amplifier of H2AK119Ub signaling

RYBP was first identified as a transcriptional corepressor that directly interacts with both RING1 and the transcription factor YY1, suggesting a role in Polycomb-mediated gene silencing [76]. Subsequent biochemical studies revealed that RYBP contains a conserved NZF domain capable of recognizing ubiquitinated substrates, including H2AK119Ub [18]. Later, a series of studies established RYBP as a defining component of vPRC1. In contrast to canonical PRC1, which harbors a CBX subunit to recognize H3K27me3, vPRC1 lacks CBX and instead utilizes the RYBP-directed recognition of H2AK119Ub for the chromatin recruitment [11,12,19,77,78]. This RYBP-based binding enables the vPRC1 complexes to be recruited to genomic sites independently of H3K27me3, thereby facilitating *de novo* establishment and spreading of Polycomb-repressed domains.

Genome-wide profiling studies of mESCs and early embryos have shown that the RYBP-harboring vPRC1 complexes often co-occupy the genomic regions marked by H3K27me3 [19,77,79]. Importantly, genetic ablation of RYBP disrupted the vPRC1 recruitment and led to the defective H3K27me3 deposition by PRC2, indicating that the RYBP-containing vPRC1 acts not only as a "reader" of H2AK119Ub but also as an important upstream regulator of PRC2 and H3K27me3 [77,79]. Besides Polycomb-targeted developmental genes, RYBP is also essential for the maintenance of silencing of inactive X chromosome during XCI. In response to Xist RNA, the PCGF3/5-containing PRC1 complexes initiate deposition of H2AK119Ub, which is subsequently "read" by the RYBP-containing vPRC1 complexes. These complexes thus amplify H2AK119Ub and facilitate the PRC2 recruitment, leading to widespread H3K27me3 deposition and chromosome-wide transcriptional repression [42]. Zhao *et al*. further demonstrated that both RYBP and its homolog YAF2 can directly recognize H2AK119Ub and, in turn, recruit RYBP/YAF2–containing vPRC1 complexes to catalyze H2AK119Ub at adjacent nucleosomes [19]. This process establishes a feedforward loop that reinforces both the formation and the spreading of Polycomb-repressed chromatin.

Recently, a high-resolution cryo-EM study elucidated the "read-write" mechanism by which the RYBP-containing vPRC1 complexes recognize the H2AK119Ub-modified nucleosomes to propagate Polycomb-mediated repression [22]. This work revealed that RYBP–PRC1 complexes engage chromatin through two distinct modes: one targeting unmodified nucleosomes and the other specifically recognizing the H2AK119Ub-modified nucleosomes (Fig. 3A). In the first mode, the RING1B–BMI1 heterodimer, which forms the catalytic core of PRC1, binds directly to the nucleosome core particle in a ubiquitin-independent manner (Fig. 3A). Here, the basic residues R81, R97, and R98 of RING1B contact the acidic patch of H2A (Fig. 3B), while BMI1 engages residues on the histones H3 and H4. This interaction is crucial for initiating H2A mono-ubiquitination. In contrast, the second binding mode—specific to H2AK119Ub-modified chromatin—is mediated by RYBP, which uses its conserved NZF domain to directly recognize the ubiquitin moiety of H2AK119Ub (Fig. 3C). A cluster of positively charged residues (R47–R56) adjacent to the NZF domain engages the acidic patch of H2A via electrostatic interactions (Fig. 3D), further stabilizing the association with modified nucleosomes. Moreover, the key residues within the NZF domain—T31, F32, and I43—interact with the I44 hydrophobic patch of ubiquitin, following a conserved interaction pattern characteristic of the Npl4-type zinc finger ubiquitin binders [80] (Fig. 3D). These two binding modes are mutually exclusive (Fig. 3E), ensuring spatial regulation of PRC1 activity. Biochemical assays demonstrated that RING1B–BMI1 binds both unmodified and H2AK119Ub-modified nucleosomes with comparable affinity, indicating that H2AK119Ub does not enhance its chromatin association [22]. In contrast, RYBP binds to the H2AK119Ub-harboring nucleosomes with nearly 10-fold higher affinity than the RING1B–BMI1 dimer, highlighting its critical role as a selective "reader" of this histone mark [22]. Such

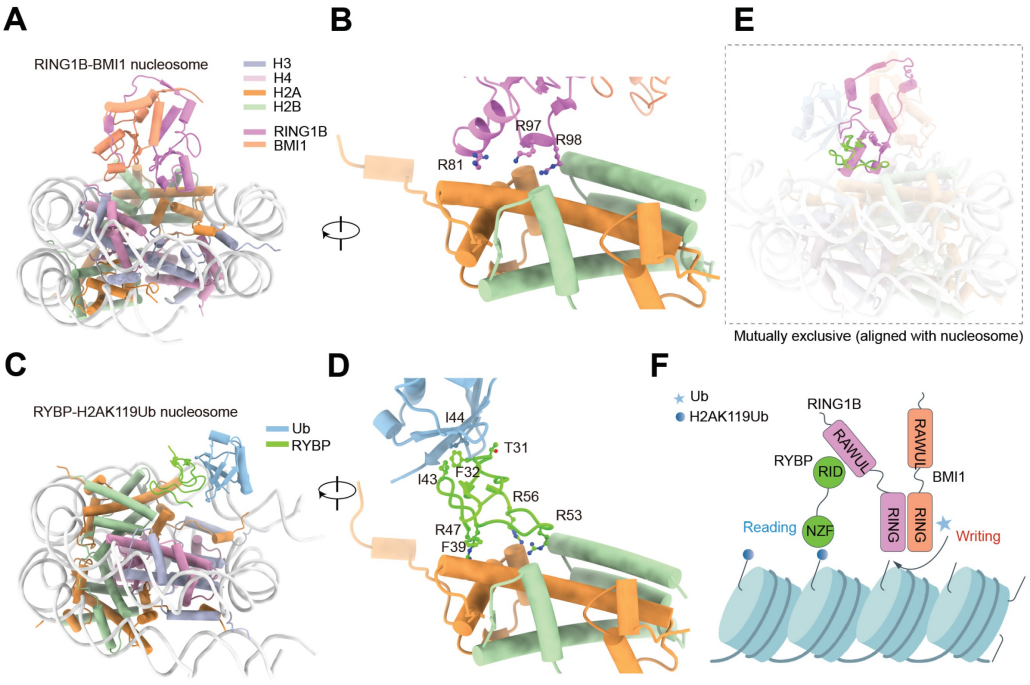

Fig. 3 A model illustrating the variant PRC1 (vPRC1)-directed "read"–"write" feedforward loop. (A, B) A structural model of the RING1B-BMI1-nucleosome (A; PDB: 8PP7), as well as a zoomed-in view (B) of the interaction between RING1B and the acidic patch of H2A. (C, D) A structural model of the RYBP-H2AK119Ub nucleosome (C; PDB: 8PP6), as well as a zoomed-in view (D) showing that the NZF domain of RYBP recognizes the H2AK119Ub-harboring nucleosome. Positively charged residues within the NZF domain interact with the H2A acidic patch, whereas a hydrophobic pocket formed by T31, F32, and I43 engages the I44 hydrophobic patch of ubiquitin. (E) Mutually exclusive binding sites of RYBP and RING1B on the nucleosome. Structural alignment indicates that RYBP and RING1B cannot simultaneously bind to the same nucleosome due to spatial clash. (F) A proposed model illustrating the "read"–"write" feedforward loop enforced by vPRC1. The catalytic subunit RING1B deposits the H2AK119Ub mark on nucleosomes ("write"), which is specifically recognized by the ubiquitin binding NZF domain of RYBP ("read"). This recognition promotes the recruitment of additional vPRC1 complexes through the interaction between the RID of RYBP and the RAWUL domain of RING1B, thereby reinforcing H2AK119Ub deposition through a self-amplifying feedforward loop. Colors and labels of protein domains, nucleosomal elements, and interaction interfaces correspond to those depicted in the figure.

preferential recognition by RYBP may explain why, in structural reconstruction of vPRC1–modified nucleosome complexes, RYBP is observed bound to H2AK119Ub-modified nucleosomes whereas the RING1B–BMI1 catalytic core is not. In addition to its NZF domain, RYBP harbors a second critical module—the RING1B-interacting domain (RID)—which directly recruits the enzymatic RING1B–BMI1 module. Based on these structural and functional insights, a positive feedback model emerges. RYBP first recognizes and anchors to the H2AK119Ub-marked nucleosomes via its NZF domain, and subsequently, through its RID, recruits RING1B–BMI1 to neighboring unmodified nucleosomes, thereby catalyzing *de novo* H2A ubiquitination (Fig. 3F, Table 1). This spatial coupling of recognition and enzymatic activity allows the RYBP-containing vPRC1 complexes to function as both "readers" and amplifiers of H2AK119Ub.

Taken together, RYBP exemplifies a dual-function chromatin effector that not only decodes but also amplifies the Polycomb-mediated gene silencing through a structurally coordinated "read-write" mechanism.

SS18::SSX onco-fusion protein "reads" H2AK119Ub, leading to aberrant activation of developmental genes and pathogenesis of synovial sarcoma

Chromatin-modifying and remodeling factors play a fundamental role in regulating DNA accessibility and transcriptional control, ensuring precise gene expression. Aberrant regulation of these factors is now appreciated to be a hallmark of human diseases, particularly cancer [81–84]. Synovial sarcoma, a rare and aggressive soft tissue sarcoma that primarily affects adolescents and young adults, provides evidence to support this principle. Nearly all cases of synovial sarcoma are driven by a disease-unique chromosomal translocation that results in the generation of an oncogenic fusion termed SS18::SSX (also known as SYT::SSX) [85–88]. This characteristic chromosomal translocation, t(X;18)(p11.2;q11.2), fuses the synovial sarcoma-associated 18 (SS18) gene on chromosome 18 to one of the synovial sarcoma X (SSX) breakpoint gene family members (most commonly SSX1 or SSX2) located on the X chromosome (Fig. 4A)

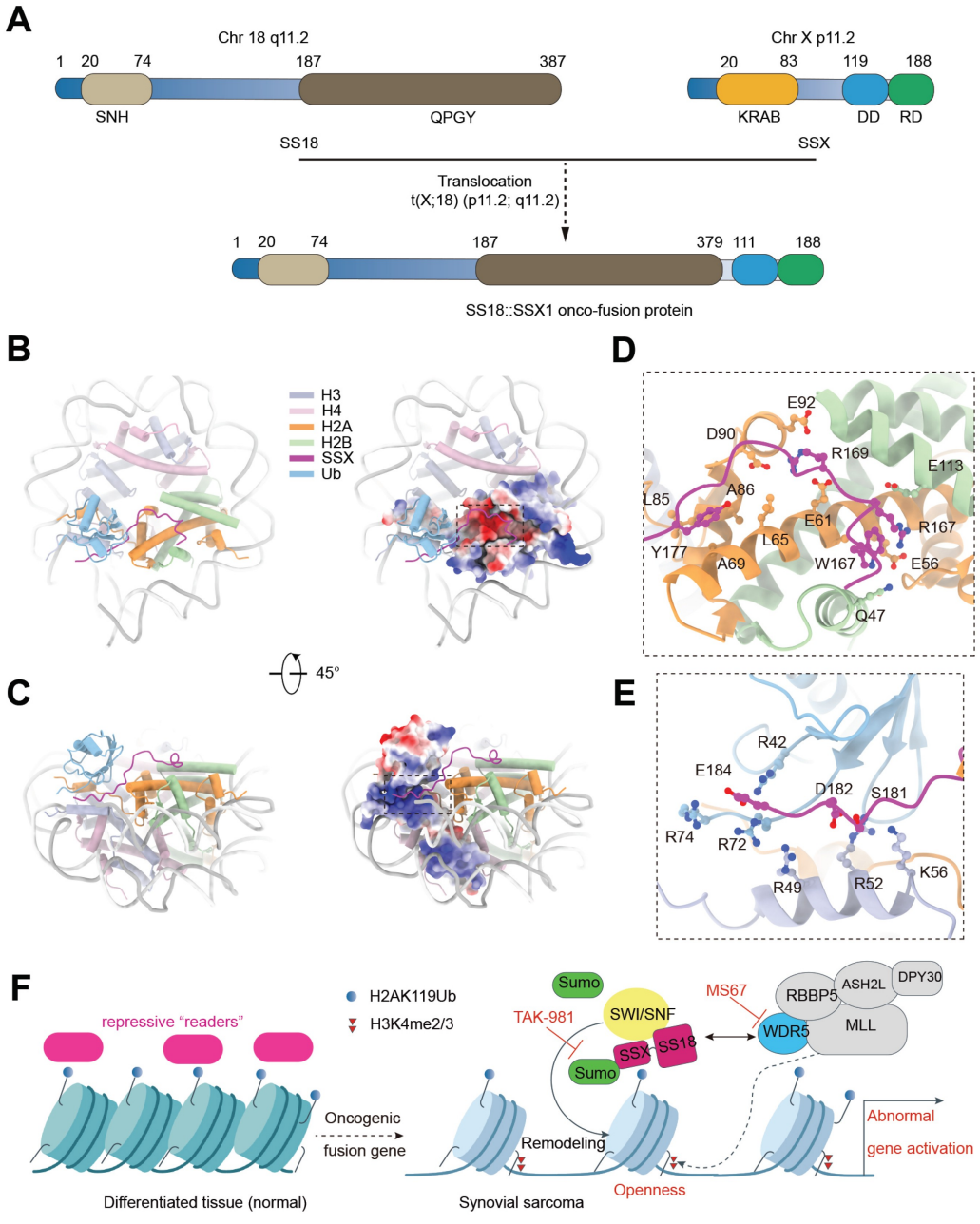

Fig. 4 A model illustrating the SSX-based "reading" of H2AK119Ub-modified nucleosomes. (A) Schematic representation of SS18::SSX, a hallmark gene translocation of synovial sarcoma. The t(X;18)(p11.2;q11.2) chromosomal translocation fuses SS18 on the chromosome 18 with SSX, generating an SS18::SSX fusion protein comprising 379 N-terminal residues from SS18 and 78 C-terminal residues from SSX. (B, C) A structural model of the SSX–H2AK119Ub nucleosome complex (PDB: 8HQY). (D, E) SSX engages the H2AK119Ub nucleosome via a bipartite recognition mechanism. The N-terminal region associates with the H2A–H2B surface (D), securing the protein to the nucleosome, while its C-terminal acidic tail docks into a basic groove formed by H3 and ubiquitin (E), thus ensuring both specific and stable recognition of the H2AK119Ub modification. (F) A model showing the SS18::SSX-mediated transcriptional dysregulation and potential therapeutic interventions. SS18::SSX hijacks coactivators (such as the ssBAF complex, the WDR-KMT2/MLL complexes, SUMO2-related modifiers, among others); the collective actions of which convert the normally repressive chromatin architecture to an activated one (featured with the increased levels of chromatin accessibility and H3K4me1/2/3 deposition), leading to oncogenic transcriptomic programs seen in synovial sarcoma. WDR5-targeting PROTACs (such as MS67) suppress the WDR-KMT2/MLL-dependent target gene activation whereas TAK-981, a SUMO2 inhibitor, restores cBAF function, thereby counteracting the SS18::SSX-driven transcriptional programs.

[86,89]. Structurally, the resultant SS18::SSX fusion combines distinct functional domains from each partner (Fig. 4A), implicating a disease-causing mechanism.

In the normal settings, SS18 acts as a component of the SWI/SNF chromatin-remodeling complex known as BRG1/BRM-associated factor (BAF) complex, which

functions to facilitate the dynamic regulation of chromatin accessibility and contributes to various processes such as normal development, cell differentiation, and cellular homeostasis [90,91]. Structurally, the normal SS18 protein (Fig. 4A) contains a transcriptional activation domain (AD) and intrinsically disordered regions (IDRs), which enable the multivalent protein–protein interactions within the BAF core complex [92]. In particular, SS18's IDR at the C terminus contains a tyrosine-rich motif termed QPGY, which has been shown to mediate formation of the nuclear condensates in a mechanism consistent with phase separation [84]. The precise role of SSX family proteins such as SSX1 and SSX2 remains incompletely defined; however, accumulating evidence suggests that SSX plays a role in epigenetic gene silencing. Structurally, the SSX protein (Fig. 4A) harbors a Krüppel associated box (KRAB)-like transcriptional repression domain (RD) at its N terminus [93], mediating interaction with co-repressors such as transducin-like enhancer 1 (TLE1) [94]. SSX's C-terminal acidic domain has been shown to colocalize with Polycomb group proteins (for example, RING1B and BMI1) [95] and contribute to formation of the repressive chromatin, again pointing to a role in transcriptional repression.

The SS18::SSX fusion protein consists of almost the entire SS18 (residues 1–379) and a C-terminal segment from SSX (residues 111–188) (Fig. 4A). Thus, SS18::SSX contains the segments of SS18 for incorporating into the BAF complex, recruiting transcriptional coactivators and inducing condensation, as well as SSX's C-terminal segment for mediating transcriptional repression and interacting with Polycomb group proteins. Therefore, the SS18::SSX fusion protein aberrantly links a gene-active SWI/SNF chromatin-remodeling complex to Polycomb repressive machinery. Indeed, SS18::SSX has been reported to disrupt the canonical BAF complex by dispelling its subunit termed SWI/SNF related BAF chromatin remodeling complex subunit B1 (SMARCB1; also known as INI1 or SNF5, which was initially identified as a TSG), resulting in the assembly of a non-canonical oncogenic BAF variant termed "ssBAF" [90]. This aberrant complex has been shown to retarget BAF complexes toward the Polycomb-bound regions where it antagonizes the PRC1 activity. Additionally, recent studies demonstrated that SS18::SSX directly recognizes H2AK119Ub, a hallmark of Polycomb-associated silencing marker, and aberrantly places the gene-active BAF complexes to the PRC1-bound loci, thereby rewiring the local gene-expression programs [92,96,97]. Recent work have further elucidated the molecular mechanism underlying SS18::SSX's targeting to the H2AK119Ub-demarcated chromatin. Its SSX moiety functions as a "reader" that binds to H2AK119Ub [98–100]. Mechanistically, the SSX region spanning the residues 162–184 adopts an extended, snake-like conformation that enables multivalent binding to the nucleosome surface [100]. This interaction is mediated through two primary interfaces that confer the chromatin binding specificity. First, a positively charged N-terminal segment of this motif interacts with the acidic patch formed by histones H2A and H2B (Fig. 4B and 4C)—a major landing "dock" for various chromatin-associated factors. In addition, the tyrosine 177 (Y177) of SSX inserts into a hydrophobic pocket composed of the α2 helix (L65 and A69) and α3 helix (L85 and A86) of H2A (Fig. 4D). Second, a negatively charged C-terminal tail of SSX was enveloped by a positively charged groove formed between H3 and ubiquitin, enabling the specifical recognition of H2AK119Ub (Fig. 4E). Mutations of the above key residues compromised SSX's ability to bind the H2AK119Ub-modified nucleosomes. Furthermore, the interaction between SSX and the H2AK119Ub-containing nucleosome also appears to promote the DNA unwrapping to some extent, a configuration associated with chromatin remodeling and regulatory factor access, which promotes chromatin accessibility and transcriptional derepression at these Polycomb-repressed loci [100]. In essence, SS18::SSX perturbs the Polycomb factors-enforced gene-silencing programs, and as a result, Polycomb factors are evicted from the H2AK119Ub-demarcated genomic regions, leading to the increased chromatin accessibility and activation of transcripts normally silenced in a developmental context [99,101]. Perturbation of such cell differentiation programs facilitates the malignant transformation (Fig. 4F and Table 1).

Early detection of synovial sarcoma is critical for effective disease treatment and improving patient outcomes. Standard treatment typically involves a combination of surgical resection [102], radiotherapy [103,104], and cytotoxic chemotherapy [105]. However, despite the aggressive multimodal therapy, the prognosis for patients with advanced or metastatic synovial sarcoma remains poor. New and more effective therapeutic strategies are needed and under active investigation [106], including immune checkpoint inhibitors, targeted therapies directed at SS18::SSX, and the SS18::SSX-associated epigenetic factors [107–110]. Proteolysis-targeting chimeras (PROTACs) represent a promising strategy for cancer therapy [111]. Selective degradation of BRD9 using PROTAC has been shown to effectively disrupt the SS18::SSX-related oncogenic transcriptional programs and suppress tumor growth *in vivo* [112,113]. Recently, Yu and colleagues demonstrated that WDR5, a core component of the KMT2/MLL H3K4 methyltransferase complexes, interacts with SS18::SSX and that synovial sarcoma exhibits an exquisite WDR5 dependency [114]. This work demonstrated existence of a previously unexplored interaction between SS18::SSX

and the WDR5-harboring KMT2/MLL complex, which deposits H3K4me3/2 and contributes to the epigenetic reprogramming driven by the fusion protein seen in synovial sarcoma. Notably, the WDR5-targeting PROTACs, such as MS67 and MS40 [114–116], selectively degraded WDR5 in synovial sarcoma, leading to downregulation of the SS18::SSX–driven oncogenic transcriptomic programs and suppression of synovial sarcoma growth *in vitro* and *in vivo* (Fig. 4F). Furthermore, independent studies reported a critical role of SUMOylation in the stabilization and/or functionality of the SS18::SSX complexes [117,118]. In essence, synovial sarcoma carrying SS18::SSX shows striking dependency on the small ubiquitin-like modifier 2 (SUMO2)-related pathway genes both *in vitro* and *in vivo*. TAK-981, a clinical-stage SUMO2 inhibitor, potently suppressed the growth of synovial sarcoma. SUMO2 inhibition by TAK-981 de-SUMOylated the cBAF subunit SMARCE1 and profoundly reduced the global protein levels and chromatin occupancy of SS18::SSX and the associated SWI/SNF complexes, leading to the repression of gene-expression programs orchestrated by the SS18::SSX onco-fusion (Fig. 4F). How SUMOylation affects the function of SS18:SSX, the associated complex, and H2AK119Ub remains to be determined. These above findings underscore the potential of targeting WDR5 through protein-degradation strategies, as well as blockade of the SUMOylation pathway using small-molecule inhibitor, for the treatment of synovial sarcoma.

Zuotin-related factor 1 (ZRF1) switches the H2AK119Ub-mediated gene silencing to activation

ZRF1, originally identified based on its homology to the yeast ribosome-associated J protein Zuotin, exhibits the functional specialization depending on its subcellular location [119,120]. In the cytosol, ZRF1 acts as a co-translational molecular chaperone, facilitating the nascent polypeptide folding and stabilizing ribosome-associated protein complexes during translation [119,120]. In contrast, the nuclear role of ZRF1 emerged with the discovery that it serves as a chromatin-associated factor capable of engaging H2AK119Ub [121].

ZRF1 is conserved and contains several functional modules [122,123] (Fig. 5A, Table 1). Its N-terminal segment harbors a DnaJ domain, a hallmark of J proteins that mediates interaction with Hsp70 chaperones. This domain is essential for ZRF1's cytosolic role in co-translational protein folding. Located downstream of the DnaJ domain is a ubiquitin binding domain (UBD), which confers the ability to recognize and bind H2AK119Ub in the nucleus. This interaction is central to ZRF1's function in chromatin regulation and transcriptional activation during cell differentiation. Structural prediction models of the ZRF1-ubquitin complex suggested that the UBD contains two potential interfaces capable of mediating this interaction (Fig. 5B). However, the detailed mechanism of recognition remains to be elucidated, particularly in the context of H2AK119Ub-modified nucleosomes.

In 2010, Richly and colleagues identified ZRF1 as a chromatin-associated factor that directly binds to H2AK119Ub using an affinity purification assay followed by mass spectrometry [121]. Through a series of deletion mapping and *in vitro* binding experiments, they further delineated that the UBD of ZRF1 is sufficient for the H2AK119Ub recognition. Surprisingly, ZRF1 and RING1B were found to compete for binding H2AK119Ub, leading to displacement of the PRC1 complex from the chromatin (Fig. 5C) [121]. This competition highlights a molecular switch during cell fate transition, in which ZRF1 effectively antagonizes Polycomb-mediated gene silencing. Indeed, ZRF1 was shown to be specifically recruited to promoters of those developmental genes repressed by Polycomb, suggesting that it acts as a key effector in relieving transcriptional repression during differentiation. Upon binding to H2AK119Ub-marked chromatin, ZRF1 can not only facilitate the displacement of PRC1 but also mediate the removal of the H2AK119Ub mark itself. This process involves cooperation with the DUB USP21 (Fig. 5C) [121]. Through this dual mechanism—eviction of PRC1 and erasure of H2AK119Ub—ZRF1 promotes the transition from a silenced chromatin state to an active one, enabling transcriptional activation of lineage-specific genes during development [121–124]. In support of this model, the induction of key developmental genes was found to be markedly impaired in ZRF1-deficient cells, underscoring ZRF1's functional requirement for reactivation of those Polycomb-regulated gene. These findings point to a context-dependent function of H2AK119Ub, depending on its "readers."

Recent studies have also linked ZRF1 to cancers. Given its ability to modulate Polycomb-mediated gene silencing, ZRF1 may function either as an oncogenic cofactor or as a tumor suppressor, depending on the cellular context and tumor type. In gastric carcinoma, ZRF1 is frequently overexpressed, correlating with aggressive features such as venous and lymphatic invasion, advanced stage, and higher recurrence rates [125]. Notably, patients with *ZRF1*-overexpressing tumors exhibit poorer outcomes. Functional studies demonstrated that *ZRF1* knockdown inhibited proliferation, migration, and invasion of gastric cancer cell lines, while inducing apoptosis in a p53-dependent manner, suggesting an oncogenic role for ZRF1. Previous studies also reported that ZRF1 is overexpressed in hematologic malignancies, including acute myeloid leukemia (AML) [126,127]. In AML, ZRF1 functions as an oncogenic epigenetic regulator,

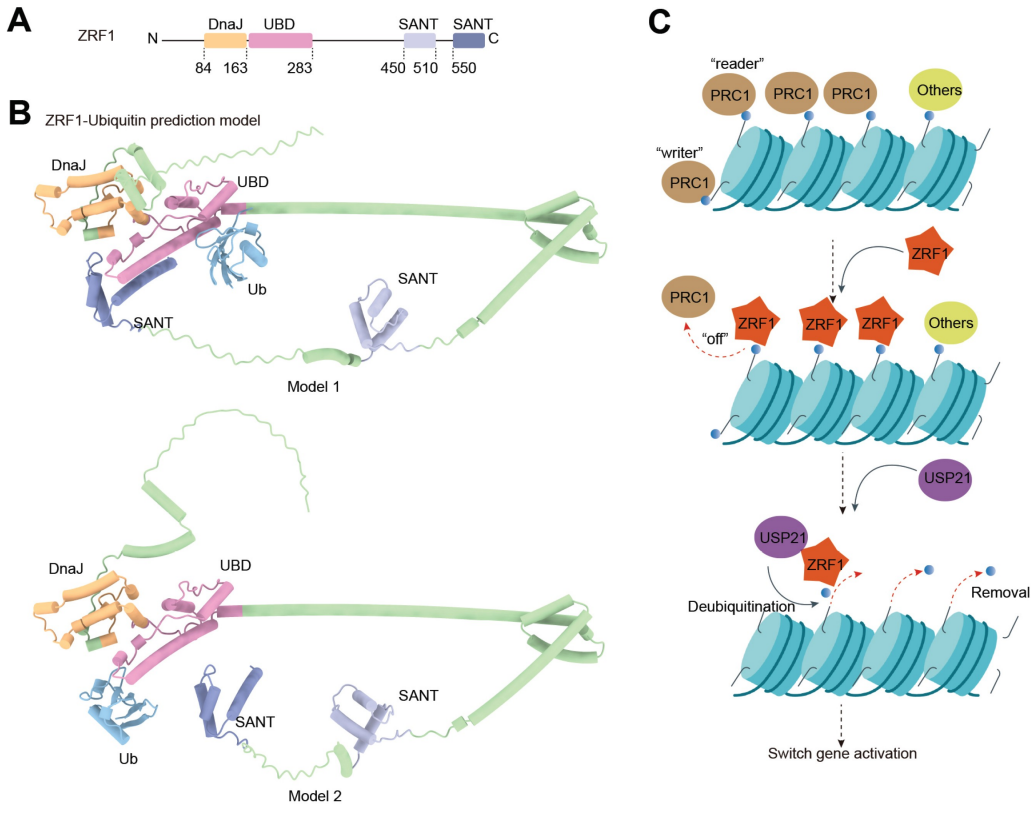

Fig. 5 A predicted model of ZRF1 binding to ubiquitin. (A) Domain organization of ZRF1, with each domain highlighted in a different color. (B) An AlphaFold-predicted structural model of ZRF1 in complex with ubiquitin. ZRF1 engages ubiquitin through its UBD, suggesting a potential mechanism for recognizing ubiquitinated chromatin. (C) A proposed model of ZRF1 function on chromatin. ZRF1 recognizes the H2AK119Ub-modified nucleosomes and displaces PRC1 from the chromatin. By recruiting the DUB USP21, ZRF1 promotes the H2AK119Ub removal, further switching the chromatin state toward transcriptional activation.

modulating transcriptional programs essential for maintaining leukemic stemness and enforcing the differentiation blockade. Mechanistic investigations revealed that ZRF1 depletion in AML led to the reduced proliferation, increased apoptosis, and enhanced myeloid differentiation. Consistently, the knockdown of *ZRF1* significantly impaired leukemia progression [127]. Importantly, ZRF1 inhibition exhibits a synergistic effect with retinoic acid (RA) therapy, highlighting a potential combinatorial approach for AML treatment. Conversely, ZRF1 also exerts tumor-suppressive effects in certain contexts. In oncogene-induced senescence, ZRF1 plays a pivotal role by activating the *INK4/ARF* locus [128]. The *INK4/ARF* activation inhibits cell proliferation and prevents malignant transformation, underscoring the role of ZRF1 as a TSG. In breast cancer, ZRF1 was reported to act as a TSG during the early stages of metastasis [129]. Together, ZRF1 has context-dependent functions. While more studies are warranted, ZRF1 has emerged as a promising biomarker of cancer progression and a potential therapeutic target in certain cancer types, particularly those exhibiting the aberrant Polycomb activity or dysregulated histone ubiquitination.

RSF1 "reads" H2AK119Ub in Polycomb-repressed chromatin

RSF1 (Table 1), a key component of the RSF chromatin-remodeling complex, was previously identified to be a "reader" of H2AK119Ub [20]. Using the approach of stable isotope labeling of amino acids in cell culture (SILAC)-based quantitative proteomics, Zhang and colleagues screened for proteins showing the preferential binding to H2AK119Ub-modified nucleosomes, and uncovered RSF1 as a H2AK119Ub binder. Subsequent functional analyses revealed that RSF1 recognizes H2AK119Ub-marked nucleosomes through a specialized ubiquitinated H2A binding (UAB) module located in its C-terminal region (residues 770–807). Chromatin immunoprecipitation profiling revealed that the RSF1 occupancy to be significantly correlated with both H2AK119Ub and Ring1B binding. Functionally, it has been reported that RSF1 repressed transcription from H2AK119Ub-modified chromatin *in vitro* and was essential for maintaining proper H2AK119Ub enrichment at the targeted regions [20]. Furthermore, RSF1 cooperates with Ring1B to regulate mesodermal patterning and gastrulation during early *Xenopus*

embryogenesis, underscoring the biological significance of this H2AK119Ub-dependent "reader" interaction [20]. These findings place RSF1 within a growing class of H2AK119Ub "reader" proteins that decode Polycomb-deposited ubiquitin signals to enforce transcriptional repression and epigenetic memory. Future structural studies will be instrumental in elucidating the precise molecular basis of RSF1's recognition of H2AK119Ub in the nucleosomal context.

H2AK119Ub signaling pathway serves as the therapeutic target

Aberrant regulation of H2AK119Ub has been implicated in various diseases such as cancer and developmental disorder, positioning this signaling axis as a promising therapeutic target. Recently, efforts have been made to modulate the activity of H2AK119Ub catalytic "writers" such as PRC1, "erasers" or DUBs such as BRCA1 associated deubiquitinase 1 (BAP1), and "readers" such as the cancer-specific SS18::SSX. In addition, innovative approaches including PROTACs and small-molecule disruptors are being employed to interfere with the H2AK119Ub–reader interactions.

PRC1 inhibitors

Unlike the much advances in developing the PRC2-specific inhibitors and next-generation degraders [130,131], the small-molecule inhibitors targeting PRC1 are currently limited. Yet, early success in inhibiting the RING1B/BMI1 catalytic core has shown high potential to suppress oncogenic functions of PRC1. It has been reported that compounds such as PTC-209 and its derivative PTC-028 reduced the expression or stability of BMI1, leading to derepression of the PRC1-silenced genes and inhibition of tumor growth [132,133]. Although these agents lack strict selectivity for RING1B/BMI1, they have demonstrated the feasibility of pharmacologically attenuating PRC1 catalytic function in diseases, marking an early success in this area. Furthermore, PROTACs designed to selectively degrade PRC1 components have been developed, providing improved specificity compared with the traditional catalytic inhibitors. For example, BMI1- or CBX8-targeting PROTACs were shown to effectively degrade PRC1 subunits, leading to decreased H2AK119Ub deposition and reactivated expression of TSGs [134,135].

DUB modulators

The H2AK119Ub homeostasis is dynamically maintained by both "writer" and "eraser" enzymes. Targeting DUBs such as BAP1 [136–138] and USP16 [23,24,139] provides an alternative route to modulate the H2AK119Ub-based signaling in diseases. Additional sex combs like 1 (ASXL1), which encodes a BAP1-interacting partner protein, is one of the most frequently mutated genes in patients with AML and other hematological cancers [140]. It has been reported that somatic mutations of ASXL1, due to its truncation and other damaging mutants targeting C-terminal region, enhance the DUB activity of the so-called ASXL-BAP1 "PR-DUB" DUB complex, removing H2AK119Ub at a global level in the cancer cells [141]. It is thus conceivable that the BAP1 inhibitors can stabilize global H2AK119Ub and enforce PRC1-mediated repression, whereas enhancing DUB activity may benefit conditions where excessive ubiquitination drives oncogenic silencing. The recently solved cryo-EM structures of BAP1-H2AK119Ub [142] and USP16-H2AK119Ub complexes [143] offer high-resolution frameworks for structure-guided drug design, which awaits further studies.

Disruption of H2AK119Ub-reader interaction

The strategies involving small molecules or peptides to disrupt the H2AK119Ub-reader binding are also being explored. Although the clinically validated compounds are not available, high-resolution structural studies of the readers bound to H2AK119Ub have revealed well-defined ubiquitin-recognition pockets that could, in principle, be exploited for inhibitor development [15,21,22,100]. In parallel, fragment-based screening efforts targeting UBDs have provided conceptual proof that such interfaces are pharmacologically tractable [144,145]. These advances highlight the potential to selectively uncouple H2AK119Ub signaling from downstream reader-mediated chromatin regulation.

Conclusions and perspectives

In recent years, H2AK119Ub has emerged as a central epigenetic mark that integrates the chromatin structure and gene/genome regulation. Once regarded as a downstream effector of PRC2, it is now recognized as a versatile signal capable of eliciting context-dependent effects, both repression and activation, through distinct "reader" proteins. These "readers" (Table 1)—including, but not limited to, JARID2, DNMT3A1, RYBP, ZRF, and RSF1—regulate a quite diverse set of biological processes, ranging from PRC2 recruitment and functionality to DNA methylation, from chromatin remodeling to transcriptional activation [15,21,22,100], and from 3D genome organization [146] to biomolecular condensation [147,148], among others, some of which are not covered in this article due to space limitations. It has been increasingly clear that the plasticity and dynamic nature of the H2AK119Ub mark underscore its functional

diversity in different chromatin environment and cellular contexts, the details of which shall represent an exciting area of investigation in the future.

Despite the above-mentioned advances, several fundamental questions remain. First, distinct H2AK119Ub "readers" engage the ubiquitinated nucleosome through the structurally similar interfaces yet elicit different regulatory outcomes. How cells selectively deploy appropriate "readers" at a given genomic locus remains unclear, which theoretically is crucial for ensuring the precise spatial and temporal control of gene expression. Factors such as the expression level, cofactor availability, and/or PTMs are all possible molecular determinants regarding the specificity in deployment of select "readers." Elucidating the underlying mechanisms will be essential for understanding how H2AK119Ub can act as a versatile regulatory platform in diverse chromatin and cellular contexts.

Second, H2AK119Ub exhibits the multi-faceted function in cells, mediating gene silencing or activation depending on which "reader" is engaged. How exactly a balance between repression and activation is maintained at these H2AK119Ub-marked genomic loci requires detailed investigation. There seems to be a consensus that H2AK119Ub mainly serves as a gene-repressive mark, recruiting Polycomb complexes, as well as DNMT3A1 in certain contexts, to reinforce target gene silencing. However, in specific contexts, H2AK119Ub is also recognized and bound by non-canonical effectors such as RSF1, which promotes chromatin remodeling and PRC1 eviction, ultimately facilitating transcriptional activation and cell-fate transitioning. The coexistence of these opposing regulatory "readers" raises a possibility that local chromatin context, combinatorial histone modifications, and/or temporal and spatial expression of "reader" proteins collectively determine the functional outcome of the H2AK119Ub recognition.

Third, the interplay between H2AK119Ub and other histone modifications remains incompletely understood. H2AK119Ub's cooperation with H3K27me3 in a Polycomb feed-forward loop is well established, yet its apparent antagonism with H3K36me2/3 suggests a more complex regulatory landscape. Insights from DNMT3A1 provide a striking example of such crosstalk. The PWWP domain of DNMT3A1 specifically recognizes H3K36me2/3 while the adjacent ADD domain binds H3K4me0, an event that releases DNMT3A1's autoinhibition, which is caused by blockade of the catalytic pocket in the absence of its cognate ligand. This combinatorial recognition ensures that DNMT3A1's activity is confined to the transcriptionally repressive chromatin and prevents aberrant DNA methylation. Intriguingly, the disease-associated DNMT3A1 mutants were found to be defective in the PWWP-mediated H3K36me2/3 recognition, lose appropriate chromatin targeting and aberrantly accumulate at the H2AK119Ub-enriched loci, underscoring a reciprocal regulatory relationship between these two histone marks. Whether H2AK119Ub engages in functional interplays with additional histone PTMs, such as H3K9me3 or histone acetylation, remains an open question and warrants further investigation.

Lastly, the recent discovery of new H2AK119Ub "readers" or coregulators has significantly expanded our current understanding of the functional readout of H2AK119Ub in biology. Traditional biochemical approaches, such as ubiquitinated nucleosome pull-down followed by mass spectrometry, have had some success in identifying high-affinity H2AK119Ub "readers." However, these methods are often insufficient to capture those low-abundance or weakly interacting "readers" that may be functionally relevant as well. The development of innovative and robust screening strategies—such as proximity labeling-based approaches or genome-wide CRISPR screens—holds a promise for uncovering the previously undetectable components in the H2AK119Ub signaling networks.

In closing, the significance of H2AK119Ub is now appreciated in quite diverse biological processes and various human diseases. We look forward to seeing more future studies aimed at unraveling how this histone PTM governs chromatin dynamics, gene expression, and cellular plasticity under both the normal and diseased settings.

Acknowledgements

We thank all members of the Wang and Cai laboratories for useful discussion. Gang Greg Wang was supported by the National Cancer Institute (NCI) grants (Nos. R01-CA271603, R01-CA268519, R01-CA296203 and R01-CA268384), and Ling Cai by the NCI grants (Nos. R01-CA262903 and R01-CA296203).

Compliance with ethics guidelines

Conflicts of interest Damu Wu, Haiqing Zhong, Ling Cai, and Gang Greg Wang declare no competing interests.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. Zhao S, Allis CD, Wang GG. The language of chromatin modification in human cancers. Nat Rev Cancer 2021; 21(7): 413–430
2. Doil C, Mailand N, Bekker-Jensen S, Menard P, Larsen DH, Pepperkok R, Ellenberg J, Panier S, Durocher D, Bartek J, Lukas J, Lukas C. RNF168 binds and amplifies ubiquitin conjugates on damaged chromosomes to allow accumulation of repair proteins. Cell 2009; 136(3): 435–446
3. Stewart GS, Panier S, Townsend K, Al-Hakim AK, Kolas NK, Miller ES, Nakada S, Ylanko J, Olivarius S, Mendez M, Oldreive C, Wildenhain J, Tagliaferro A, Pelletier L, Taubenheim N, Durandy A, Byrd PJ, Stankovic T, Taylor AM, Durocher D. The RIDDLE syndrome protein mediates a ubiquitin-dependent signaling cascade at sites of DNA damage. Cell 2009; 136(3): 420–434
4. Mattiroli F, Vissers JH, van Dijk WJ, Ikpa P, Citterio E, Vermeulen W, Marteijn JA, Sixma TK. RNF168 ubiquitinates K13-15 on H2A/H2AX to drive DNA damage signaling. Cell 2012; 150(6): 1182–1195
5. Fradet-Turcotte A, Canny MD, Escribano-Díaz C, Orthwein A, Leung CC, Huang H, Landry MC, Kitevski-LeBlanc J, Noordermeer SM, Sicheri F, Durocher D. 53BP1 is a reader of the DNA-damage-induced H2A Lys 15 ubiquitin mark. Nature 2013; 499(7456): 50–54
6. Kalb R, Mallery DL, Larkin C, Huang JT, Hiom K. BRCA1 is a histone-H2A-specific ubiquitin ligase. Cell Rep 2014; 8(4): 999–1005
7. Mattiroli F, Penengo L. Histone ubiquitination: an integrative signaling platform in genome stability. Trends Genet 2021; 37(6): 566–581
8. Sekiguchi M, Matsushita N. DNA damage response regulation by histone ubiquitination. Int J Mol Sci 2022; 23(15): 8187
9. Wang H, Wang L, Erdjument-Bromage H, Vidal M, Tempst P, Jones RS, Zhang Y. Role of histone H2A ubiquitination in Polycomb silencing. Nature 2004; 431(7010): 873–878
10. Stock JK, Giadrossi S, Casanova M, Brookes E, Vidal M, Koseki H, Brockdorff N, Fisher AG, Pombo A. Ring1-mediated ubiquitination of H2A restrains poised RNA polymerase II at bivalent genes in mouse ES cells. Nat Cell Biol 2007; 9(12): 1428–1435
11. Gao Z, Zhang J, Bonasio R, Strino F, Sawai A, Parisi F, Kluger Y, Reinberg D. PCGF homologs, CBX proteins, and RYBP define functionally distinct PRC1 family complexes. Mol Cell 2012; 45(3): 344–356
12. Tavares L, Dimitrova E, Oxley D, Webster J, Poot R, Demmers J, Bezstarosti K, Taylor S, Ura H, Koide H, Wutz A, Vidal M, Elderkin S, Brockdorff N. RYBP-PRC1 complexes mediate H2A ubiquitylation at polycomb target sites independently of PRC2 and H3K27me3. Cell 2012; 148(4): 664–678
13. Blackledge NP, Farcas AM, Kondo T, King HW, McGouran JF, Hanssen LLP, Ito S, Cooper S, Kondo K, Koseki Y, Ishikura T, Long HK, Sheahan TW, Brockdorff N, Kessler BM, Koseki H, Klose RJ. Variant PRC1 complex-dependent H2A ubiquitylation drives PRC2 recruitment and polycomb domain formation. Cell 2014; 157(6): 1445–1459
14. Cooper S, Grijzenhout A, Underwood E, Ancelin K, Zhang T, Nesterova TB, Anil-Kirmizitas B, Bassett A, Kooistra SM, Agger K, Helin K, Heard E, Brockdorff N. Jarid2 binds mono-ubiquitylated H2A lysine 119 to mediate crosstalk between Polycomb complexes PRC1 and PRC2. Nat Commun 2016; 7(1): 13661
15. Chen X, Guo Y, Zhao T, Lu J, Fang J, Wang Y, Wang GG, Song J. Structural basis for the H2AK119ub1-specific DNMT3A-nucleosome interaction. Nat Commun 2024; 15(1): 6217
16. Gretarsson KH, Abini-Agbomson S, Gloor SL, Weinberg DN, McCuiston JL, Kumary VUS, Hickman AR, Sahu V, Lee R, Xu X, Lipieta N, Flashner S, Adeleke OA, Popova IK, Taylor HF, Noll K, Windham CL, Maryanski DN, Venters BJ, Nakagawa H, Keogh MC, Armache KJ, Lu C. Cancer-associated DNA hypermethylation of Polycomb targets requires DNMT3A dual recognition of histone H2AK119 ubiquitination and the nucleosome acidic patch. Sci Adv 2024; 10(35): eadp0975
17. Wapenaar H, Clifford G, Rolls W, Pasquier M, Burdett H, Zhang Y, Deák G, Zou J, Spanos C, Taylor MRD, Mills J, Watson JA, Kumar D, Clark R, Das A, Valsakumar D, Bramham J, Voigt P, Sproul D, Wilson MD. The N-terminal region of DNMT3A engages the nucleosome surface to aid chromatin recruitment. EMBO Rep 2024; 25(12): 5743–5779
18. Arrigoni R, Alam SL, Wamstad JA, Bardwell VJ, Sundquist WI, Schreiber-Agus N. The Polycomb-associated protein Rybp is a ubiquitin binding protein. FEBS Lett 2006; 580(26): 6233–6241
19. Zhao J, Wang M, Chang L, Yu J, Song A, Liu C, Huang W, Zhang T, Wu X, Shen X, Zhu B, Li G. RYBP/YAF2-PRC1 complexes and histone H1-dependent chromatin compaction mediate propagation of H2AK119ub1 during cell division. Nat Cell Biol 2020; 22(4): 439–452
20. Zhang Z, Jones AE, Wu W, Kim J, Kang Y, Bi X, Gu Y, Popov IK, Renfrow MB, Vassylyeva MN, Vassylyev DG, Giles KE, Chen D, Kumar A, Fan Y, Tong Y, Liu CF, An W, Chang C, Luo J, Chow LT, Wang H. Role of remodeling and spacing factor 1 in histone H2A ubiquitination-mediated gene silencing. Proc Natl Acad Sci USA 2017; 114(38): E7949–E7958
21. Kasinath V, Beck C, Sauer P, Poepsel S, Kosmatka J, Faini M, Toso D, Aebersold R, Nogales E. JARID2 and AEBP2 regulate PRC2 in the presence of H2AK119ub1 and other histone modifications. Science 2021; 371(6527): eabc3393
22. Ciapponi M, Karlukova E, Schkölziger S, Benda C, Müller J. Structural basis of the histone ubiquitination read-write mechanism of RYBP-PRC1. Nat Struct Mol Biol 2024; 31(7): 1023–1027
23. Adorno M, Sikandar S, Mitra SS, Kuo A, Nicolis Di Robilant B, Haro-Acosta V, Ouadah Y, Quarta M, Rodriguez J, Qian D, Reddy VM, Cheshier S, Garner CC, Clarke MF. Usp16 contributes to somatic stem-cell defects in Down's syndrome. Nature 2013; 501(7467): 380–384

24. Gu Y, Jones AE, Yang W, Liu S, Dai Q, Liu Y, Swindle CS, Zhou D, Zhang Z, Ryan TM, Townes TM, Klug CA, Chen D, Wang H. The histone H2A deubiquitinase Usp16 regulates hematopoiesis and hematopoietic stem cell function. Proc Natl Acad Sci USA 2016; 113(1): E51–E60
25. Haugh AM, Njauw CN, Bubley JA, Verzì AE, Zhang B, Kudalkar E, VandenBoom T, Walton K, Swick BL, Kumar R, Rana HQ, Cochrane S, McCormick SR, Shea CR, Tsao H, Gerami P. Genotypic and phenotypic features of BAP1 cancer syndrome: a report of 8 new families and review of cases in the literature. JAMA Dermatol 2017; 153(10): 999–1006
26. Liu W, Zeng Y, Hao X, Wang X, Liu J, Gao T, Wang M, Zhang J, Huo M, Hu T, Ma T, Zhang D, Teng X, Yu H, Zhang M, Yuan B, Huang W, Yang Y, Wang Y. JARID2 coordinates with the NuRD complex to facilitate breast tumorigenesis through response to adipocyte-derived leptin. Cancer Commun (Lond) 2023; 43(10): 1117–1142
27. Celik H, Koh WK, Kramer AC, Ostrander EL, Mallaney C, Fisher DAC, Xiang J, Wilson WC, Martens A, Kothari A, Fishberger G, Tycksen E, Karpova D, Duncavage EJ, Lee Y, Oh ST, Challen GA. JARID2 functions as a tumor suppressor in myeloid neoplasms by repressing self-renewal in hematopoietic progenitor cells. Cancer Cell 2018; 34(5): 741–756.e8
28. 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(10): 1211–1222
29. Lee Y, Song AJ, Baker R, Micales B, Conway SJ, Lyons GE. Jumonji, a nuclear protein that is necessary for normal heart development. Circ Res 2000; 86(9): 932–938
30. Li G, Margueron R, Ku M, Chambon P, Bernstein BE, Reinberg D. Jarid2 and PRC2, partners in regulating gene expression. Genes Dev 2010; 24(4): 368–380
31. Takeuchi T, Watanabe Y, Takano-Shimizu T, Kondo S. Roles of jumonji and jumonji family genes in chromatin regulation and development. Dev Dyn 2006; 235(9): 2449–2459
32. Kim TG, Kraus JC, Chen J, Lee Y. JUMONJI, a critical factor for cardiac development, functions as a transcriptional repressor. J Biol Chem 2003; 278(43): 42247–42255
33. Kim TG, Chen J, Sadoshima J, Lee Y. Jumonji represses atrial natriuretic factor gene expression by inhibiting transcriptional activities of cardiac transcription factors. Mol Cell Biol 2004; 24(23): 10151–10160
34. Landeira D, Sauer S, Poot R, Dvorkina M, Mazzarella L, Jørgensen HF, Pereira CF, Leleu M, Piccolo FM, Spivakov M, Brookes E, Pombo A, Fisher C, Skarnes WC, Snoek T, Bezstarosti K, Demmers J, Klose RJ, Casanova M, Tavares L, Brockdorff N, Merkenschlager M, Fisher AG. Jarid2 is a PRC2 component in embryonic stem cells required for multi-lineage differentiation and recruitment of PRC1 and RNA Polymerase II to developmental regulators. Nat Cell Biol 2010; 12(6): 618–624
35. Pasini D, Cloos PA, Walfridsson J, Olsson L, Bukowski JP, Johansen JV, Bak M, Tommerup N, Rappsilber J, Helin K. JARID2 regulates binding of the Polycomb repressive complex 2 to target genes in ES cells. Nature 2010; 464(7286): 306–310
36. Guo Y, Zhao S, Wang GG. Polycomb gene silencing mechanisms: PRC2 chromatin targeting, H3K27me3 'readout', and phase separation-based compaction. Trends Genet 2021; 37(6): 547–565
37. Piunti A, Shilatifard A. The roles of Polycomb repressive complexes in mammalian development and cancer. Nat Rev Mol Cell Biol 2021; 22(5): 326–345
38. Margueron R, Reinberg D. The Polycomb complex PRC2 and its mark in life. Nature 2011; 469(7330): 343–349
39. Blackledge NP, Klose RJ. The molecular principles of gene regulation by Polycomb repressive complexes. Nat Rev Mol Cell Biol 2021; 22(12): 815–833
40. Kalb R, Latwiel S, Baymaz HI, Jansen PW, Müller CW, Vermeulen M, Müller J. Histone H2A monoubiquitination promotes histone H3 methylation in Polycomb repression. Nat Struct Mol Biol 2014; 21(6): 569–571
41. da Rocha ST, Boeva V, Escamilla-Del-Arenal M, Ancelin K, Granier C, Matias NR, Sanulli S, Chow J, Schulz E, Picard C, Kaneko S, Helin K, Reinberg D, Stewart AF, Wutz A, Margueron R, Heard E. Jarid2 is implicated in the initial xist-induced targeting of PRC2 to the inactive X chromosome. Mol Cell 2014; 53(2): 301–316
42. Almeida M, Pintacuda G, Masui O, Koseki Y, Gdula M, Cerase A, Brown D, Mould A, Innocent C, Nakayama M, Schermelleh L, Nesterova TB, Koseki H, Brockdorff N. PCGF3/5-PRC1 initiates Polycomb recruitment in X chromosome inactivation. Science 2017; 356(6342): 1081–1084
43. Verberne EA, Goh S, England J, van Ginkel M, Rafael-Croes L, Maas S, Polstra A, Zarate YA, Bosanko KA, Pechter KB, Bedoukian E, Izumi K, Chaudhry A, Robin NH, Boothe M, Lippa NC, Aggarwal V, De Vivo DC, Lehman A, Study C, Stockler S, Bruel AL, Isidor B, Lemons J, Rodriguez-Buritica DF, Richmond CM, Stark Z, Agrawal PB, Kooy RF, Meuwissen MEC, Koolen DA, Pfundt R, Lieden A, Anderlid BM, Glatz D, Mannens MMAM, Bakshi M, Mallette FA, van Haelst MM, Campeau PM. JARID2 haploinsufficiency is associated with a clinically distinct neurodevelopmental syndrome. Genet Med 2021; 23(2): 374–383
44. Cadieux-Dion M, Farrow E, Thiffault I, Cohen ASA, Welsh H, Bartik L, Schwager C, Engleman K, Zhou D, Zhang L, Repnikova E, Amudhavalli SM, Saunders CJ. Phenotypic expansion and variable expressivity in individuals with JARID2-related intellectual disability: a case series. Clin Genet 2022; 102(2): 136–141
45. Barøy T, Misceo D, Strømme P, Stray-Pedersen A, Holmgren A, Rødningen OK, Blomhoff A, Helle JR, Stormyr A, Tvedt B, Fannemel M, Frengen E. Haploinsufficiency of two histone modifier genes on 6p22.3, ATXN1 and JARID2, is associated with intellectual disability. Orphanet J Rare Dis 2013; 8(1): 3
46. Sreeshma B, Devi A. JARID2 and EZH2, the eminent epigenetic drivers in human cancer. Gene 2023; 879: 147584
47. Tange S, Oktyabri D, Terashima M, Ishimura A, Suzuki T. JARID2 is involved in transforming growth factor-beta-induced epithelial-mesenchymal transition of lung and colon cancer cell lines. PLoS One 2014; 9(12): e115684
48. Song J, Teplova M, Ishibe-Murakami S, Patel DJ. Structure-based mechanistic insights into DNMT1-mediated maintenance DNA methylation. Science 2012; 335(6069): 709–712
49. Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for *de novo* methylation and mammalian development. Cell 1999; 99(3): 247–257
50. Baubec T, Colombo DF, Wirbelauer C, Schmidt J, Burger L,

Krebs AR, Akalin A, Schübeler D. Genomic profiling of DNA methyltransferases reveals a role for DNMT3B in genic methylation. Nature 2015; 520(7546): 243–247

51. Morselli M, Pastor WA, Montanini B, Nee K, Ferrari R, Fu K, Bonora G, Rubbi L, Clark AT, Ottonello S, Jacobsen SE, Pellegrini M. *In vivo* targeting of *de novo* DNA methylation by histone modifications in yeast and mouse. eLife 2015; 4: e06205
52. Manzo M, Wirz J, Ambrosi C, Villaseñor R, Roschitzki B, Baubec T. Isoform-specific localization of DNMT3A regulates DNA methylation fidelity at bivalent CpG islands. EMBO J 2017; 36(23): 3421–3434
53. Chen T, Ueda Y, Xie S, Li E. A novel Dnmt3a isoform produced from an alternative promoter localizes to euchromatin and its expression correlates with active *de novo* methylation. J Biol Chem 2002; 277(41): 38746–38754
54. Weisenberger DJ, Velicescu M, Preciado-Lopez MA, Gonzales FA, Tsai YC, Liang G, Jones PA. Identification and characterization of alternatively spliced variants of DNA methyltransferase 3a in mammalian cells. Gene 2002; 298(1): 91–99
55. Chen T, Ueda Y, Dodge JE, Wang Z, Li E. Establishment and maintenance of genomic methylation patterns in mouse embryonic stem cells by Dnmt3a and Dnmt3b. Mol Cell Biol 2003; 23(16): 5594–5605
56. La Salle S, Trasler JM. Dynamic expression of DNMT3a and DNMT3b isoforms during male germ cell development in the mouse. Dev Biol 2006; 296(1): 71–82
57. Chen BF, Chan WY. The *de novo* DNA methyltransferase DNMT3A in development and cancer. Epigenetics 2014; 9(5): 669–677
58. Dukatz M, Holzer K, Choudalakis M, Emperle M, Lungu C, Bashtrykov P, Jeltsch A. H3K36me2/3 binding and DNA binding of the DNA methyltransferase DNMT3A PWWP domain both contribute to its chromatin interaction. J Mol Biol 2019; 431(24): 5063–5074
59. Weinberg DN, Papillon-Cavanagh S, Chen H, Yue Y, Chen X, Rajagopalan KN, Horth C, McGuire JT, Xu X, Nikbakht H, Lemiesz AE, Marchione DM, Marunde MR, Meiners MJ, Cheek MA, Keogh MC, Bareke E, Djedid A, Harutyunyan AS, Jabado N, Garcia BA, Li H, Allis CD, Majewski J, Lu C. The histone mark H3K36me2 recruits DNMT3A and shapes the intergenic DNA methylation landscape. Nature 2019; 573(7773): 281–286
60. Dhayalan A, Rajavelu A, Rathert P, Tamas R, Jurkowska RZ, Ragozin S, Jeltsch A. The Dnmt3a PWWP domain reads histone 3 lysine 36 trimethylation and guides DNA methylation. J Biol Chem 2010; 285(34): 26114–26120
61. Otani J, Nankumo T, Arita K, Inamoto S, Ariyoshi M, Shirakawa M. Structural basis for recognition of H3K4 methylation status by the DNA methyltransferase 3A ATRX-DNMT3-DNMT3L domain. EMBO Rep 2009; 10(11): 1235–1241
62. Guo X, Wang L, Li J, Ding Z, Xiao J, Yin X, He S, Shi P, Dong L, Li G, Tian C, Wang J, Cong Y, Xu Y. Structural insight into autoinhibition and histone H3-induced activation of DNMT3A. Nature 2015; 517(7536): 640–644
63. Li BZ, Huang Z, Cui QY, Song XH, Du L, Jeltsch A, Chen P, Li G, Li E, Xu GL. Histone tails regulate DNA methylation by allosterically activating *de novo* methyltransferase. Cell Res 2011; 21(8): 1172–1181
64. Gao L, Emperle M, Guo Y, Grimm SA, Ren W, Adam S, Uryu H, Zhang ZM, Chen D, Yin J, Dukatz M, Anteneh H, Jurkowska RZ, Lu J, Wang Y, Bashtrykov P, Wade PA, Wang GG, Jeltsch A, Song J. Comprehensive structure-function characterization of DNMT3B and DNMT3A reveals distinctive *de novo* DNA methylation mechanisms. Nat Commun 2020; 11(1): 3355
65. Jia D, Jurkowska RZ, Zhang X, Jeltsch A, Cheng X. Structure of Dnmt3a bound to Dnmt3L suggests a model for *de novo* DNA methylation. Nature 2007; 449(7159): 248–251
66. Zhang ZM, Lu R, Wang P, Yu Y, Chen D, Gao L, Liu S, Ji D, Rothbart SB, Wang Y, Wang GG, Song J. Structural basis for DNMT3A-mediated *de novo* DNA methylation. Nature 2018; 554(7692): 387–391
67. Rolls W, Wilson MD, Sproul D. Using human disease mutations to understand *de novo* DNA methyltransferase function. Biochem Soc Trans 2024; 52(5): 2059–2075
68. Weinberg DN, Rosenbaum P, Chen X, Barrows D, Horth C, Marunde MR, Popova IK, Gillespie ZB, Keogh MC, Lu C, Majewski J, Allis CD. Two competing mechanisms of DNMT3A recruitment regulate the dynamics of *de novo* DNA methylation at PRC1-targeted CpG islands. Nat Genet 2021; 53(6): 794–800
69. McGinty RK, Tan S. Principles of nucleosome recognition by chromatin factors and enzymes. Curr Opin Struct Biol 2021; 71: 16–26
70. Mohn F, Weber M, Rebhan M, Roloff TC, Richter J, Stadler MB, Bibel M, Schübeler D. Lineage-specific polycomb targets and *de novo* DNA methylation define restriction and potential of neuronal progenitors. Mol Cell 2008; 30(6): 755–766
71. Fu K, Bonora G, Pellegrini M. Interactions between core histone marks and DNA methyltransferases predict DNA methylation patterns observed in human cells and tissues. Epigenetics 2020; 15(3): 272–282
72. Heyn P, Logan CV, Fluteau A, Challis RC, Auchynnikava T, Martin CA, Marsh JA, Taglini F, Kilanowski F, Parry DA, Cormier-Daire V, Fong CT, Gibson K, Hwa V, Ibáñez L, Robertson SP, Sebastiani G, Rappsilber J, Allshire RC, Reijns MAM, Dauber A, Sproul D, Jackson AP. Gain-of-function DNMT3A mutations cause microcephalic dwarfism and hypermethylation of Polycomb-regulated regions. Nat Genet 2019; 51(1): 96–105
73. Kibe K, Shirane K, Ohishi H, Uemura S, Toh H, Sasaki H. The DNMT3A PWWP domain is essential for the normal DNA methylation landscape in mouse somatic cells and oocytes. PLoS Genet 2021; 17(5): e1009570
74. Sendžikaitė G, Hanna CW, Stewart-Morgan KR, Ivanova E, Kelsey G. A DNMT3A PWWP mutation leads to methylation of bivalent chromatin and growth retardation in mice. Nat Commun 2019; 10(1): 1884
75. Mellid S, Coloma J, Calsina B, Monteagudo M, Roldán-Romero JM, Santos M, Leandro-García LJ, Lanillos J, Martínez-Montes ÁM, Rodríguez-Antona C, Montero-Conde C, Martínez-López J, Ayala R, Matias-Guiu X, Robledo M, Cascón A. Novel *DNMT3A* germline variant in a patient with multiple paragangliomas and papillary thyroid carcinoma. Cancers (Basel) 2020; 12(11): 3304
76. García E, Marcos-Gutiérrez C, del Mar Lorente M, Moreno JC, Vidal M. RYBP, a new repressor protein that interacts with components of the mammalian Polycomb complex, and with the transcription factor YY1. EMBO J 1999; 18(12): 3404–3418

77. Rose NR, King HW, Blackledge NP, Fursova NA, Ember KJ, Fischer R, Kessler BM, Klose RJ. RYBP stimulates PRC1 to shape chromatin-based communication between Polycomb repressive complexes. eLife 2016; 5: e18591
78. Cohen I, Bar C, Ezhkova E. Activity of PRC1 and histone H2AK119 monoubiquitination: revising popular misconceptions. BioEssays 2020; 42(5): 1900192
79. Tamburri S, Lavarone E, Fernández-Pérez D, Conway E, Zanotti M, Manganaro D, Pasini D. Histone H2AK119 mono-ubiquitination is essential for Polycomb-mediated transcriptional repression. Mol Cell 2020; 77(4): 840–856.e5
80. Alam SL, Sun J, Payne M, Welch BD, Blake BK, Davis DR, Meyer HH, Emr SD, Sundquist WI. Ubiquitin interactions of NZF zinc fingers. EMBO J 2004; 23(7): 1411–1421
81. Kadoch C, Williams RT, Calarco JP, Miller EL, Weber CM, Braun SM, Pulice JL, Chory EJ, Crabtree GR. Dynamics of BAF-Polycomb complex opposition on heterochromatin in normal and oncogenic states. Nat Genet 2017; 49(2): 213–222
82. Huang C, Sloan EA, Boerkoel CF. Chromatin remodeling and human disease. Curr Opin Genet Dev 2003; 13(3): 246–252
83. Cho KS, Elizondo LI, Boerkoel CF. Advances in chromatin remodeling and human disease. Curr Opin Genet Dev 2004; 14(3): 308–315
84. Kuang J, Zhai Z, Li P, Shi R, Guo W, Yao Y, Guo J, Zhao G, He J, Xu S, Wu C, Yu S, Zhou C, Wu L, Qin Y, Cai B, Li W, Wu Z, Li X, Chu S, Yang T, Wang B, Cao S, Li D, Zhang X, Chen J, Liu J, Pei D. SS18 regulates pluripotent-somatic transition through phase separation. Nat Commun 2021; 12(1): 4090
85. Clark J, Rocques PJ, Crew AJ, Gill S, Shipley J, Chan AM, Gusterson BA, Cooper CS. Identification of novel genes, SYT and SSX, involved in the t(X;18)(p11.2;q11.2) translocation found in human synovial sarcoma. Nat Genet 1994; 7(4): 502–508
86. Ladanyi M, Antonescu CR, Leung DH, Woodruff JM, Kawai A, Healey JH, Brennan MF, Bridge JA, Neff JR, Barr FG, Goldsmith JD, Brooks JS, Goldblum JR, Ali SZ, Shipley J, Cooper CS, Fisher C, Skytting B, Larsson O. Impact of SYT-SSX fusion type on the clinical behavior of synovial sarcoma: a multi-institutional retrospective study of 243 patients. Cancer Res 2002; 62(1): 135–140
87. Fisher C. Synovial sarcoma. Ann Diagn Pathol 1998; 2(6): 401–421
88. Ladanyi M. Fusions of the SYT and SSX genes in synovial sarcoma. Oncogene 2001; 20(40): 5755–5762
89. Crew AJ, Clark J, Fisher C, Gill S, Grimer R, Chand A, Shipley J, Gusterson BA, Cooper CS. Fusion of SYT to two genes, SSX1 and SSX2, encoding proteins with homology to the Kruppel-associated box in human synovial sarcoma. EMBO J 1995; 14(10): 2333–2340
90. Kadoch C, Crabtree GR. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. Cell 2013; 153(1): 71–85
91. Ho L, Jothi R, Ronan JL, Cui K, Zhao K, Crabtree GR. An embryonic stem cell chromatin remodeling complex, esBAF, is an essential component of the core pluripotency transcriptional network. Proc Natl Acad Sci USA 2009; 106(13): 5187–5191
92. Mashtalir N, D'Avino AR, Michel BC, Luo J, Pan J, Otto JE, Zullow HJ, McKenzie ZM, Kubiak RL, St Pierre R, Valencia AM, Poynter SJ, Cassel SH, Ranish JA, Kadoch C. Modular organization and assembly of SWI/SNF family chromatin remodeling complexes. Cell 2018; 175(5): 1272–1288.e20
93. Lim FL, Soulez M, Koczan D, Thiesen HJ, Knight JC. A KRAB-related domain and a novel transcription repression domain in proteins encoded by SSX genes that are disrupted in human sarcomas. Oncogene 1998; 17(15): 2013–2018
94. Soulez M, Saurin AJ, Freemont PS, Knight JC. SSX and the synovial-sarcoma-specific chimaeric protein SYT-SSX co-localize with the human Polycomb group complex. Oncogene 1999; 18(17): 2739–2746
95. dos Santos NR, de Bruijn DR, Kater-Baats E, Otte AP, van Kessel AG. Delineation of the protein domains responsible for SYT, SSX, and SYT-SSX nuclear localization. Exp Cell Res 2000; 256(1): 192–202
96. Banito A, Li X, Laporte AN, Roe JS, Sanchez-Vega F, Huang CH, Dancsok AR, Hatzi K, Chen CC, Tschaharganeh DF, Chandwani R, Tasdemir N, Jones KB, Capecchi MR, Vakoc CR, Schultz N, Ladanyi M, Nielsen TO, Lowe SW. The SS18-SSX oncoprotein hijacks KDM2B-PRC1.1 to drive synovial sarcoma. Cancer Cell 2018; 33(3): 527–541.e8
97. McBride MJ, Pulice JL, Beird HC, Ingram DR, D'Avino AR, Shern JF, Charville GW, Hornick JL, Nakayama RT, Garcia-Rivera EM, Araujo DM, Wang WL, Tsai JW, Yeagley M, Wagner AJ, Futreal PA, Khan J, Lazar AJ, Kadoch C. The SS18-SSX fusion oncoprotein hijacks BAF complex targeting and function to drive synovial sarcoma. Cancer Cell 2018; 33(6): 1128–1141.e7
98. McBride MJ, Mashtalir N, Winter EB, Dao HT, Filipovski M, D' Avino AR, Seo HS, Umbreit NT, St Pierre R, Valencia AM, Qian K, Zullow HJ, Jaffe JD, Dhe-Paganon S, Muir TW, Kadoch C. The nucleosome acidic patch and H2A ubiquitination underlie mSWI/SNF recruitment in synovial sarcoma. Nat Struct Mol Biol 2020; 27(9): 836–845
99. Benabdallah NS, Dalal V, Scott RW, Marcous F, Sotiriou A, Kommoss FKF, Pejkovska A, Gaspar L, Wagner L, Sánchez-Rivera FJ, Ta M, Thornton S, Nielsen TO, Underhill TM, Banito A. Aberrant gene activation in synovial sarcoma relies on SSX specificity and increased PRC1.1 stability. Nat Struct Mol Biol 2023; 30(11): 1640–1652
100. Tong Z, Ai H, Xu Z, He K, Chu GC, Shi Q, Deng Z, Xue Q, Sun M, Du Y, Liang L, Li JB, Pan M, Liu L. Synovial sarcoma X breakpoint 1 protein uses a cryptic groove to selectively recognize H2AK119Ub nucleosomes. Nat Struct Mol Biol 2024; 31(2): 300–310
101. Michel BC, D'Avino AR, Cassel SH, Mashtalir N, McKenzie ZM, McBride MJ, Valencia AM, Zhou Q, Bocker M, Soares LMM, Pan J, Remillard DI, Lareau CA, Zullow HJ, Fortoul N, Gray NS, Bradner JE, Chan HM, Kadoch C. A non-canonical SWI/SNF complex is a synthetic lethal target in cancers driven by BAF complex perturbation. Nat Cell Biol 2018; 20(12): 1410–1420
102. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Conrad EU 3rd, Ganjoo KN, George S, Gonzalez RJ, Heslin MJ, Kane JM 3rd, Koon H, Mayerson J, McCarter M, McGarry SV, Meyer C, O'Donnell RJ, Pappo AS, Paz IB, Petersen IA, Pfeifer JD, Riedel RF, Schuetze S, Schupak KD, Schwartz HS, Tap WD, Wayne JD, Bergman MA, Scavone J. Soft tissue sarcoma, version

2.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016; 14(6): 758–786

103. Gingrich AA, Marrufo AS, Liu Y, Li CS, Darrow MA, Monjazeb AM, Thorpe SW, Canter RJ. Radiotherapy is associated with improved survival in patients with synovial sarcoma undergoing surgery: a national cancer database analysis. J Surg Res 2020; 255: 378–387
104. Gingrich AA, Bateni SB, Monjazeb AM, Darrow MA, Thorpe SW, Kirane AR, Bold RJ, Canter RJ. Neoadjuvant Radiotherapy is associated with R0 resection and improved survival for patients with extremity soft tissue sarcoma undergoing surgery: a national cancer database analysis. Ann Surg Oncol 2017; 24(11): 3252–3263
105. Stacchiotti S, Van Tine BA. Synovial sarcoma: current concepts and future perspectives. J Clin Oncol 2018; 36(2): 180–187
106. El Beaino M, Rassy E, Hadid B, Araujo DM, Pavlidis N, Lin PP. Synovial sarcoma: a complex disease with multifaceted signaling and epigenetic landscapes. Curr Oncol Rep 2020; 22(12): 124
107. Su L, Sampaio AV, Jones KB, Pacheco M, Goytain A, Lin S, Poulin N, Yi L, Rossi FM, Kast J, Capecchi MR, Underhill TM, Nielsen TO. Deconstruction of the SS18-SSX fusion oncoprotein complex: insights into disease etiology and therapeutics. Cancer Cell 2012; 21(3): 333–347
108. Lubieniecka JM, de Bruijn DR, Su L, van Dijk AH, Subramanian S, van de Rijn M, Poulin N, van Kessel AG, Nielsen TO. Histone deacetylase inhibitors reverse SS18-SSX-mediated polycomb silencing of the tumor suppressor early growth response 1 in synovial sarcoma. Cancer Res 2008; 68(11): 4303–4310
109. Laporte AN, Poulin NM, Barrott JJ, Wang XQ, Lorzadeh A, Vander Werff R, Jones KB, Underhill TM, Nielsen TO. Death by HDAC Inhibition in synovial sarcoma cells. Mol Cancer Ther 2017; 16(12): 2656–2667
110. Laporte AN, Ji JX, Ma L, Nielsen TO, Brodin BA. Identification of cytotoxic agents disrupting synovial sarcoma oncoprotein interactions by proximity ligation assay. Oncotarget 2016; 7(23): 34384–34394
111. Burslem GM, Crews CM. Proteolysis-targeting chimeras as therapeutics and tools for biological discovery. Cell 2020; 181(1): 102–114
112. Remillard D, Buckley DL, Paulk J, Brien GL, Sonnett M, Seo HS, Dastjerdi S, Wühr M, Dhe-Paganon S, Armstrong SA, Bradner JE. Degradation of the BAF complex factor BRD9 by heterobifunctional ligands. Angew Chem Int Ed Engl 2017; 56(21): 5738–5743
113. Brien GL, Remillard D, Shi J, Hemming ML, Chabon J, Wynne K, Dillon ET, Cagney G, Van Mierlo G, Baltissen MP, Vermeulen M, Qi J, Fröhling S, Gray NS, Bradner JE, Vakoc CR, Armstrong SA. Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma. eLife 2018; 7: e41305
114. Yu Y, Yu X, Pan B, Chan HM, Kaniskan HU, Jin J, Cai L, Wang GG. Pharmacologic degradation of WDR5 suppresses oncogenic activities of SS18: SSX and provides a therapeutic of synovial sarcoma. Sci Adv 2025; 11(17): eads7876
115. Li D, Yu X, Kottur J, Gong W, Zhang Z, Storey AJ, Tsai YH, Uryu H, Shen Y, Byrum SD, Edmondson RD, Mackintosh SG, Cai L, Liu Z, Aggarwal AK, Tackett AJ, Liu J, Jin J, Wang GG. Discovery of a dual WDR5 and Ikaros PROTAC degrader as an anti-cancer therapeutic. Oncogene 2022; 41(24): 3328–3340
116. Yu X, Li D, Kottur J, Shen Y, Kim HS, Park KS, Tsai YH, Gong W, Wang J, Suzuki K, Parker J, Herring L, Kaniskan HÜ, Cai L, Jain R, Liu J, Aggarwal AK, Wang GG, Jin J. A selective WDR5 degrader inhibits acute myeloid leukemia in patient-derived mouse models. Sci Transl Med 2021; 13(613): eabj1578
117. Iyer R, Deshpande A, Pedgaonkar A, Bala PA, Kim T, Brien GL, Finlay D, Vuori K, Soragni A, Wetterstein HI, Murad R, Deshpande AJ. Targeting SUMO2 reverses aberrant epigenetic rewiring driven by SS18: SSX fusion oncoproteins and impairs sarcomagenesis. EMBO J 2025; 44(18): 4984–5004
118. Floros KV, Fairchild CK, Li J, Zhang K, Roberts JL, Kurupi R, Hu B, Kraskauskiene V, Hosseini N, Shen S, Inge MM, Smith-Fry K, Li L, Sotiriou A, Dalton KM, Jose A, Abdelfadiel EI, Xing Y, Hill RD, Slaughter JM, Shende M, Lorenz MR, Hinojosa MR, Belvin BR, Lai Z, Boikos SA, Stamatouli AM, Lewis JP, Manjili MH, Valerie K, Li R, Banito A, Poklepovic A, Koblinski JE, Siggers T, Dozmorov MG, Jones KB, Radhakrishnan SK, Faber AC. Targeting of SUMOylation leads to cBAF complex stabilization and disruption of the SS18: SSX transcriptome in synovial sarcoma. bioRxiv. 2024; 6: rs.3.rs–4362092
119. Hundley HA, Walter W, Bairstow S, Craig EA. Human Mpp11 J protein: ribosome-tethered molecular chaperones are ubiquitous. Science 2005; 308(5724): 1032–1034
120. Lee K, Sharma R, Shrestha OK, Bingman CA, Craig EA. Dual interaction of the Hsp70 J-protein cochaperone Zuotin with the 40S and 60S ribosomal subunits. Nat Struct Mol Biol 2016; 23(11): 1003–1010
121. Richly H, Rocha-Viegas L, Ribeiro JD, Demajo S, Gundem G, Lopez-Bigas N, Nakagawa T, Rospert S, Ito T, Di Croce L. Transcriptional activation of polycomb-repressed genes by ZRF1. Nature 2010; 468(7327): 1124–1128
122. Aloia L, Demajo S, Di Croce L. ZRF1: a novel epigenetic regulator of stem cell identity and cancer. Cell Cycle 2015; 14(4): 510–515
123. Feng J, Gao Y, Wang K, Jiang M. A novel epigenetic regulator ZRF1: insight into its functions in plants. Genes (Basel) 2021; 12(8): 1245
124. Richly H, Di Croce L. The flip side of the coin: role of ZRF1 and histone H2A ubiquitination in transcriptional activation. Cell Cycle 2011; 10(5): 745–750
125. Imamura T, Komatsu S, Ichikawa D, Miyamae M, Okajima W, Ohashi T, Kiuchi J, Nishibeppu K, Kosuga T, Konishi H, Shiozaki A, Fujiwara H, Okamoto K, Tsuda H, Otsuji E. Overexpression of ZRF1 is related to tumor malignant potential and a poor outcome of gastric carcinoma. Carcinogenesis 2018; 39(2): 263–271
126. Siegel S, Wirth S, Schweizer M, Schmitz N, Zeis M. M-phase phosphoprotein 11 is a highly immunogenic tumor antigen in patients with acute myeloid leukemia. Acta Haematol 2012; 127(4): 193–197
127. Demajo S, Uribesalgo I, Gutiérrez A, Ballaré C, Capdevila S, Roth M, Zuber J, Martín-Caballero J, Di Croce L. ZRF1 controls the retinoic acid pathway and regulates leukemogenic potential in acute myeloid leukemia. Oncogene 2014; 33(48): 5501–5510
128. Ribeiro JD, Morey L, Mas A, Gutierrez A, Luis NM, Mejetta S, Richly H, Benitah SA, Keyes WM, Di Croce L. ZRF1 controls oncogene-induced senescence through the INK4-ARF locus.

Oncogene 2013; 32(17): 2161–2168
129. Kaymak A, Sayols S, Papadopoulou T, Richly H. Role for the transcriptional activator ZRF1 in early metastatic events in breast cancer progression and endocrine resistance. Oncotarget 2018; 9(47): 28666–28690
130. Xu B, Konze KD, Jin J, Wang GG. Targeting EZH2 and PRC2 dependence as novel anticancer therapy. Exp Hematol 2015; 43(8): 698–712
131. Wang J, Yu X, Gong W, Liu X, Park KS, Ma A, Tsai YH, Shen Y, Onikubo T, Pi WC, Allison DF, Liu J, Chen WY, Cai L, Roeder RG, Jin J, Wang GG. EZH2 noncanonically binds cMyc and p300 through a cryptic transactivation domain to mediate gene activation and promote oncogenesis. Nat Cell Biol 2022; 24(3): 384–399
132. Mayr C, Wagner A, Loeffelberger M, Bruckner D, Jakab M, Berr F, Di Fazio P, Ocker M, Neureiter D, Pichler M, Kiesslich T. The BMI1 inhibitor PTC-209 is a potential compound to halt cellular growth in biliary tract cancer cells. Oncotarget 2016; 7(1): 745–758
133. Dey A, Xiong X, Crim A, Dwivedi SKD, Mustafi SB, Mukherjee P, Cao L, Sydorenko N, Baiazitov R, Moon YC, Dumble M, Davis T, Bhattacharya R. Evaluating the mechanism and therapeutic potential of PTC-028, a novel inhibitor of BMI-1 function in ovarian cancer. Mol Cancer Ther 2018; 17(1): 39–49
134. Park KS, Qin L, Kabir M, Luo K, Dale B, Zhong Y, Kim A, Wang GG, Kaniskan HÜ, Jin J. Targeted degradation of PRC1 components, BMI1 and RING1B, via a novel protein complex degrader strategy. Adv Sci (Weinh) 2023; 10(10): 2205573
135. Suh JL, Bsteh D, Hart B, Si Y, Weaver TM, Pribitzer C, Lau R, Soni S, Ogana H, Rectenwald JM, Norris JL, Cholensky SH, Sagum C, Umana JD, Li D, Hardy B, Bedford MT, Mumenthaler SM, Lenz HJ, Kim YM, Wang GG, Pearce KH, James LI, Kireev DB, Musselman CA, Frye SV, Bell O. Reprogramming CBX8-PRC1 function with a positive allosteric modulator. Cell Chem Biol 2022; 29(4): 555–571.e11
136. Campagne A, Lee MK, Zielinski D, Michaud A, Le Corre S, Dingli F, Chen H, Shahidian LZ, Vassilev I, Servant N, Loew D, Pasmant E, Postel-Vinay S, Wassef M, Margueron R. BAP1 complex promotes transcription by opposing PRC1-mediated H2A ubiquitylation. Nat Commun 2019; 10(1): 348
137. Conway E, Rossi F, Fernandez-Perez D, Ponzo E, Ferrari KJ, Zanotti M, Manganaro D, Rodighiero S, Tamburri S, Pasini D. BAP1 enhances Polycomb repression by counteracting widespread H2AK119ub1 deposition and chromatin condensation. Mol Cell 2021; 81(17): 3526–3541.e8
138. Fursova NA, Turberfield AH, Blackledge NP, Findlater EL, Lastuvkova A, Huseyin MK, Dobrinić P, Klose RJ. BAP1 constrains pervasive H2AK119ub1 to control the transcriptional potential of the genome. Genes Dev 2021; 35(9-10): 749–770
139. Yang W, Lee YH, Jones AE, Woolnough JL, Zhou D, Dai Q, Wu Q, Giles KE, Townes TM, Wang H. The histone H2A deubiquitinase Usp16 regulates embryonic stem cell gene expression and lineage commitment. Nat Commun 2014; 5(1): 3818
140. Asada S, Fujino T, Goyama S, Kitamura T. The role of ASXL1 in hematopoiesis and myeloid malignancies. Cell Mol Life Sci 2019; 76(13): 2511–2523
141. Dong Z, Sepulveda H, Arteaga-Vazquez LJ, Blouin C, Fernandez J, Binder M, Chou WC, Tien HF, Patnaik MM, Faulkner GJ, Myers SA, Rao A. A mutant ASXL1-BAP1-EHMT complex contributes to heterochromatin dysfunction in clonal hematopoiesis and chronic monomyelocytic leukemia. Proc Natl Acad Sci USA 2025; 122(1): e2413302121
142. Ge W, Yu C, Li J, Yu Z, Li X, Zhang Y, Liu CP, Li Y, Tian C, Zhang X, Li G, Zhu B, Xu RM. Basis of the H2AK119 specificity of the Polycomb repressive deubiquitinase. Nature 2023; 616(7955): 176–182
143. Ai H, He Z, Deng Z, Chu GC, Shi Q, Tong Z, Li JB, Pan M, Liu L. Structural and mechanistic basis for nucleosomal H2AK119 deubiquitination by single-subunit deubiquitinase USP16. Nat Struct Mol Biol 2024; 31(11): 1745–1755
144. Loh YY, Anantharajan J, Huang Q, Xu W, Fulwood J, Ng HQ, Ng EY, Gea CY, Choong ML, Tan QW, Koh X, Lim WH, Nacro K, Cherian J, Baburajendran N, Ke Z, Kang C. Identification of small-molecule binding sites of a ubiquitin-conjugating enzyme-UBE2T through fragment-based screening. Protein Sci 2024; 33(3): e4904
145. Ernst A, Avvakumov G, Tong J, Fan Y, Zhao Y, Alberts P, Persaud A, Walker JR, Neculai AM, Neculai D, Vorobyov A, Garg P, Beatty L, Chan PK, Juang YC, Landry MC, Yeh C, Zeqiraj E, Karamboulas K, Allali-Hassani A, Vedadi M, Tyers M, Moffat J, Sicheri F, Pelletier L, Durocher D, Raught B, Rotin D, Yang J, Moran MF, Dhe-Paganon S, Sidhu SS. A strategy for modulation of enzymes in the ubiquitin system. Science 2013; 339(6119): 590–595
146. Guo Y, Wang GG. Modulation of the high-order chromatin structure by Polycomb complexes. Front Cell Dev Biol 2022; 10: 1021658
147. Xu C, Kim A, Corbin JM, Wang GG. Onco-condensates: formation, multi-component organization, and biological functions. Trends Cancer 2023; 9(9): 738–751
148. Brown K, Chew PY, Ingersoll S, Espinosa JR, Aguirre A, Espinoza A, Wen J, Astatike K, Kutateladze TG, Collepardo-Guevara R, Ren X. Principles of assembly and regulation of condensates of Polycomb repressive complex 1 through phase separation. Cell Rep 2023; 42(10): 113136