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Review

Cite this article: Lane KA, Harrod A, Downs J. 2025 Boundary issues: SWI/SNF shapes chromatin patterns in and around centromeres. *Open Biol.* **15**: 250186.
https://doi.org/10.1098/rsob.250186

Received: 30 May 2025
Accepted: 29 October 2025

Subject Areas:
cellular biology, bioinformatics

Keywords:
SWI/SNF, chromatin, centromeres, PBAF, PBRM1, heterochromatin, chromosome instability

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Boundary issues: SWI/SNF shapes chromatin patterns in and around centromeres

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The SWI/SNF family of chromatin remodelling complexes, comprising BAF, PBAF and ncBAF, is known for their critical roles in regulating chromatin accessibility and gene expression in mammalian cells. Recent advances have shed light on a function for SWI/SNF complexes, particularly PBAF, at centromeres. In this review, we explore the emerging roles of SWI/SNF complexes in safeguarding centromere stability and discuss how disruption of PBAF leads to centromere fragility. We propose that PBAF contributes to the establishment and maintenance of boundaries between heterochromatin and euchromatin regions within centromeres and pericentromeres, thus contributing to their overall architecture. By preserving these boundaries, PBAF ensures the functional integrity of centromeres, which is essential for faithful chromosome segregation.

1. Centromere and pericentromere organization

The centromere is a defined, specialized chromosomal region that enables assembly of the kinetochore in dividing cells, allowing equal and accurate transmission of genetic information to daughter cells. Human centromeres are defined at the DNA level by highly repetitive sequences known as alpha-satellite (α-satellite) sequences arranged into tandem arrays known as higher-order repeats (HORs; figure 1a) [1,2]. At the chromatin level, the functional region of the centromere is characterized by the incorporation of the histone H3 variant CENP-A (centromere protein A) into nucleosomes [3], which appears more essential for centromere formation than α-satellite DNA as it can be incorporated into nucleosomes in a sequence-independent manner [4,5]. CENP-A-containing chromatin interacts with the inner kinetochore or CCAN (constitutive centromere-associated network), a group of 16 CENPs, centromere proteins which serve as a structural base for assembly of the kinetochore during cell division [6,7] (reviewed in [8]). In vertebrates, centromeric DNA also contains sequence motifs known as CENP-B boxes, which allow direct binding to DNA of CENP-B, a protein that also interacts with CENP-A and CENP-C of the CCAN [9,10]. While not essential, CENP-B ensures correct compaction and clustering of centromeric DNA by promoting the formation of loops, and its loss leads to chromosome missegregation [10,11]. Numerous other secondary structures can also form in the centromere due to its repetitive nature, such as hairpins, cruciform structures, R-loops and i-motifs [12–16], further deepening the complexity of this region and likely improving its stability.

While the CCAN and therefore the kinetochore generally assembles onto a single active HOR on each chromosome, this region represents only a proportion of the entire centromeric structure. The decompacted and flexible HOR is surrounded by the more heterogenous pericentromere (figure 1a). The pericentromere includes inactive α-satellite arrays such as divergent HORs, HSATs (human satellites) and transposable elements (TEs) [2,16].

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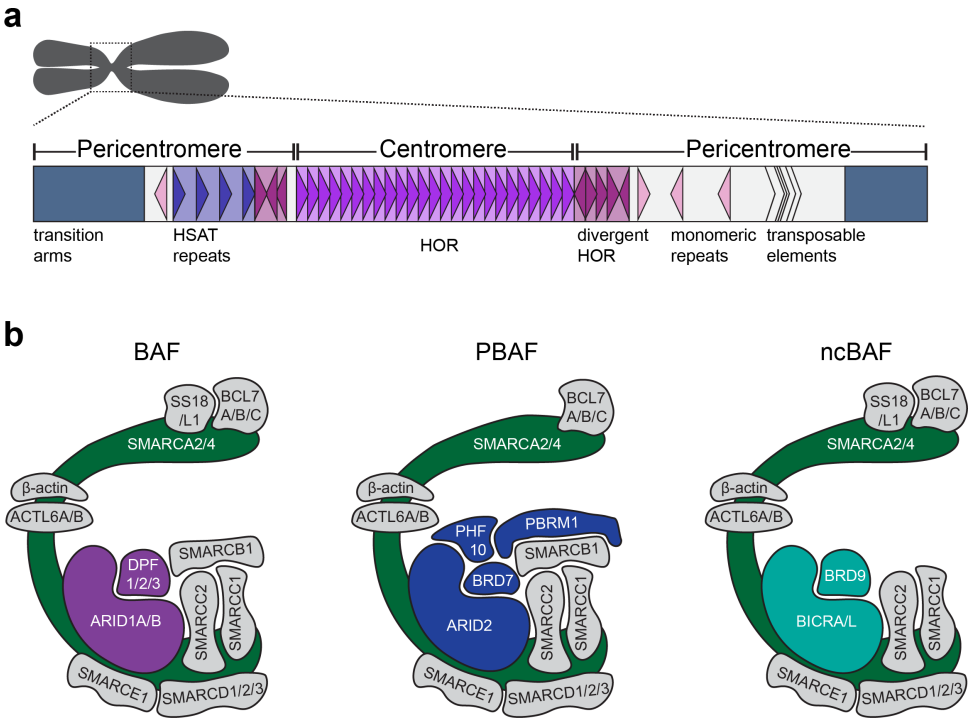


Figure 1. Centromere and SWI/SNF composition in cells. (a) Schematic indicating a typical composition of the centromere in human chromosomes, with the active core centromeric region formed of arrays of higher-order repeats (HORs), while the more heterogeneous pericentric heterochromatin is formed of shorter and more diverse arrays such as divergent HORs, monomeric satellites and transposable elements, as well as the transition arms between the pericentromere and the flanking chromosomal arms. (b) Schematic showing the subunit composition of the three primary SWI/SNF complexes: BAF, PBAF and non-canonical BAF (ncBAF).

The pericentromere also contains the centric transition regions—non-satellite DNA largely made up of segmental duplications found between satellite regions and extending into the p- and q-arms of chromosomes, forming a boundary between the centromere and the non-centromeric, gene-coding regions of the chromosome [17,18]. The centromeric (HOR) and pericentromeric regions of the centromere are epigenetically defined by distinct histone modifications, such as H3K36me2/3, H4K20me and H3K9ac at the HOR versus H3K9me2/3 and H3K27me2/3 in the pericentromere, reviewed in [19] and described below. While in the past the centromere was thought of as a transcriptionally inactive site, it is now known that this region is transcribed at a low level, and much of this transcription is important for centromere function. This is especially true within the HOR, as this region is enriched with activating histone marks and has lower levels of CpG methylation. In general, the centromere transcribes long non-coding RNAs (cen-lncRNAs) rather than protein-coding genes, and these cen-lncRNAs are retained and bound by centromeres and appear to be important for its stability [20]. The pericentromere, however, contains regions of highly inaccessible heterochromatic DNA, associated with transcriptional repression and compact chromatin, interspersed with some areas of open chromatin, including protein-coding genes [21,22].

2. Centromere stability

Maintenance of centromere stability and structure is essential for faithful cell division, and therefore genome stability, and perturbations at the centromere can lead to aneuploidy or structural variations in daughter cells (reviewed in [23]). However, the repetitive nature of centromeric DNA makes it a particularly fragile site, prone to breaks and recombination, especially during replication and cell division (reviewed in [24]). Aneuploidy has been recognized as a hallmark of cancer for decades [25], and chromosomal instability (CIN) as a result of chromosome missegregation is observed across almost all tumour types [26].

Conversely, the high level of DNA breakage and resultant activation of DNA repair mechanisms in centromeric regions may also contribute to the high level of variability between centromeres and their rapidly evolving nature [2,27–30], suggesting that DNA breaks and recombination are also functionally important at the centromere. Neocentromeres—centromeres that form de novo at ectopic sites—are also associated with disease, primarily cancer and congenital abnormalities (reviewed in [31]). Neocentromeres can form at sites without α-satellite arrays or CENP-B box motifs via the incorporation of CENP-A into nucleosomes [32], enabling the binding of CCAN proteins and kinetochore formation. Interestingly, neocentromeres tend to form in euchromatic regions [33], but the formation of a neocentromere leads to the spreading of repressive heterochromatic marks to form compact chromatin resembling the pericentromere, likely improving the stability and rigidity of the neocentromere and maintaining a tight boundary between pericentric regions and the active HOR region [34]. Concurrently, H3K9me3 marks are removed from the active neocentromeric region, leading to the expansion and stabilization of the CENP-A region of the centromere, further indicating that heterochromatin forms a barrier for maintaining the core centromeric region [35]. CENP-A is also overexpressed and mislocalized in many cancers without the formation of neocentromeres, and this dysregulation contributes to genome instability [35,36].

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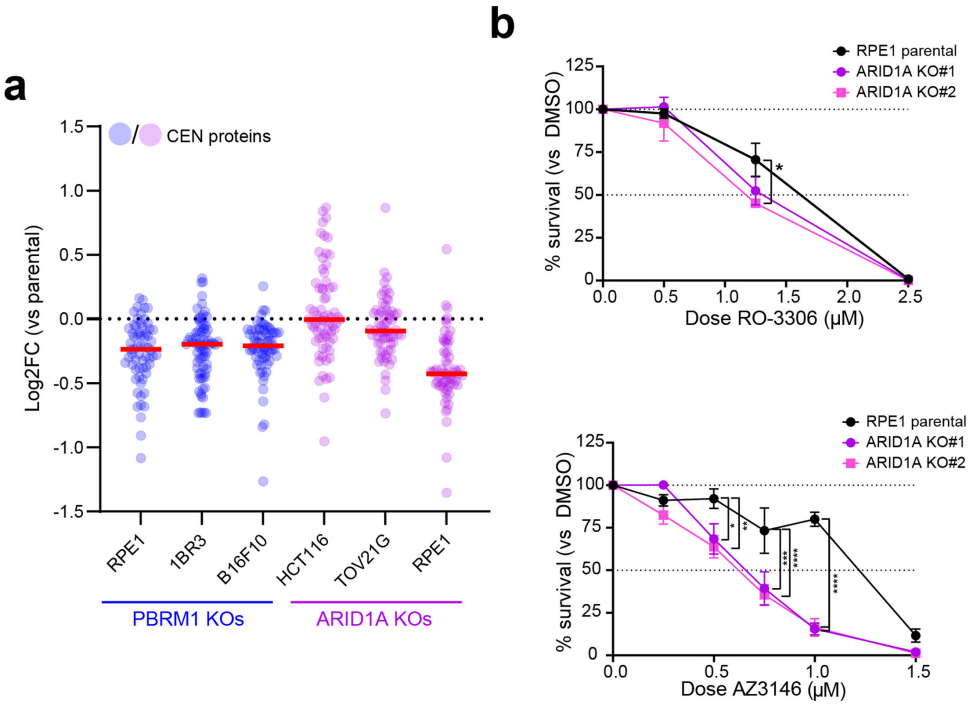


Figure 2. PBAF loss affects centromeric protein abundance, but this is not as prevalent following BAF perturbation. (a) Log2 fold change (Log2FC) of centromere- and pericentromere-associated proteins in PBRM1 (blue) and ARID1A (purple) knockouts compared to their corresponding parental cells, with the exception of TOV21G, where ARID1A-deficient parental cells were compared to cells stably expressing an ARID1A construct. Points correspond to the median Log2FC of multiple biological replicates and knockout clones, with a line at the median of all protein Log2FCs. Data accessible from the PRoteomics IDEntification Database (PRIDE) under accession numbers PXD043209 for PBRM1 KOs [48] and PXD063556 for ARID1A KOs [49]. (b) Clonogenic survival of RPE1 parental and ARID1A knockouts when treated with increasing doses of the CDK1 inhibitor RO-3306 (left, $n = 5$) or the Mps1 inhibitor AZ3146 (right, $n = 4$), relative to DMSO-only treated cells. Data are presented as mean ± s.e.m. and were analysed using a two-way ANOVA with Dunnett's test, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$.

3. SWI/SNF and centromere function

While epigenetic mechanisms such as histone modifications and DNA methylation play a key role in proper centromere specification and function, ATP-dependent chromatin remodelling complexes have also been implicated. The NoRC complex, a member of the ISWI family of chromatin remodellers comprising TIP5 and SMARCA5 (also known as SNF2H), is important for maintaining pericentric heterochromatin (PHC) and therefore satellite stability [37]. Another ISWI complex, RSF, made up of RSF1 and SMARCA5, contributes to CENP-A incorporation into centromeric nucleosomes and regulates histone modifications at centromeres during cell division [38,39]. In addition, a growing body of evidence links the SWI/SNF family of chromatin remodelling complexes to centromere and pericentromere maintenance.

The SWI/SNF family is made up of three major complexes—BAF, PBAF and ncBAF—which share common subunits but also have complex-specific subunits (figure 1b). SWI/SNF mutations occur in over 20% of all cancers (reviewed in [40]), and the loss-of-function mutations are generally considered important for tumourigenesis. In fission yeast, loss of the RSC complex, homologous to PBAF, leads to centromeric defects and ectopic spreading of CENP-A into PHC [41,42]. Budding yeast SWI/SNF, more closely related to BAF, provides a similar role [43]. In human cells, a genetic screen identified two core SWI/SNF subunits, ACTL6B and SMARCD3, as regulators of CENP-A stability [44], suggesting that SWI/SNF may play a role in centromere stability and maintenance.

PBRM1, an SWI/SNF complex subunit specific to the PBAF complex, is frequently mutated in cancer, particularly in clear cell renal cell carcinoma, where more than 40% of cancers have loss-of-function mutations in PBRM1 (reviewed in [40]). Loss of PBRM1 has multiple cellular functions that are relevant for tumourigenesis, including impaired DNA repair [40], transcriptional dysregulation [45] and increased inflammatory signalling after DNA damage [46]. Cells deficient in PBRM1 have previously been shown to have impaired sister chromatid cohesion and increased incidence of aneuploidy and chromosomal aberrations, suggesting that genome instability in PBRM1-deficient cells could be arising at least in part from mitotic or centromeric defects [47].

Recently, we found that loss of PBRM1 leads to centromeric fragility, which explains the increased incidence of whole-arm chromosomal rearrangements rather than intra-arm breaks, as well as DNA recombination between sister centromeres [48], demonstrating a role for PBRM1 and the PBAF complex in the maintenance of centromere stability. Loss of PBRM1 was correlated with decreased abundance of centromere-associated proteins (figure 2a) [48], including CCAN components and PHC-associated proteins. However, this loss was not accompanied by changes in the levels of centromere gene transcripts, leading us to hypothesize that the decreased abundance was instead due to a perturbation of the underlying chromatin structure (discussed in more detail below).

One question arising from these studies is whether there is any redundancy between the SWI/SNF complexes at centromeres. ARID1A is a subunit specific to the BAF complex, and when analysing these same centromere-associated proteins in several

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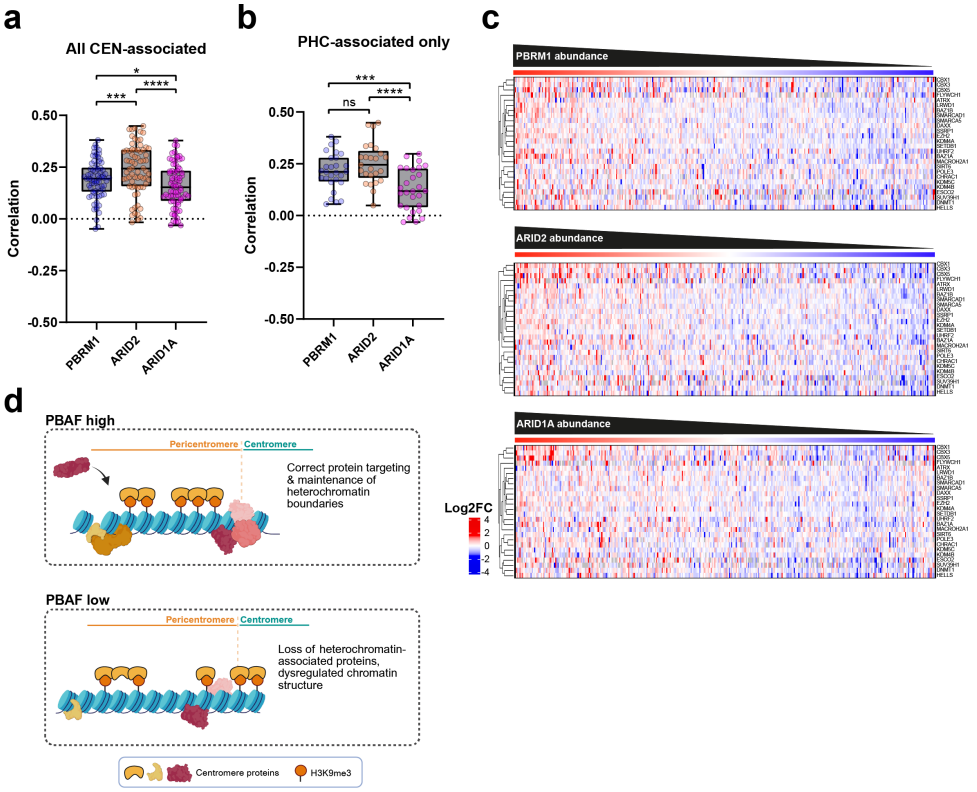


Figure 3. PBAF levels positively correlate with the abundance of pericentric heterochromatic proteins across cancer cell lines. (a) Pearson correlation of log2 fold changes (Log2FCs) of centromere- and pericentromere-associated proteins versus Log2FCs of SWI/SNF proteins PBRM1, ARID2 and ARID1A, in cancer cell lines from the CCLE database. Points correspond to individual proteins as in figure 2a. (b) Pearson correlation of Log2FCs of pericentromere-associated proteins only versus SWI/SNF proteins PBRM1 (blue), ARID2 (orange) and ARID1A (purple), in cancer cell lines from the CCLE database. For both (a) and (b), data are plotted as minimum to maximum with a line at median, and data were analysed using a paired *t*-test, $*p < 0.05$, $***p < 0.001$, $****p < 0.0001$. (c) Heatmap of Log2FCs of pericentromere-associated proteins in cancer cell lines from the CCLE database. Columns represent individual cell lines, and rows show Log2FCs of indicated pericentric heterochromatic (PHC) proteins. Heatmaps are ordered from highest to lowest Log2FCs of PBRM1 (top), ARID2 (middle) and ARID1A (bottom). (d) Schematic summarizing the correlation between PBAF levels and pericentromere stability. Created in BioRender.

ARID1A knockout cells, this reduction in CENP levels was only observed in a single cell line (figure 2a); yet this cell line did not exhibit a concurrent development of centromere recombination and fragility [48]. These cells did, however, exhibit sensitivity to mitotic perturbation via treatment with CDK1 or Mps1 inhibitors (figure 2b), leading to the intriguing possibility that there is a different form of centromere instability in ARID1A-deficient cells. This is perhaps related to kinetochore attachment or cell division, rather than in the underlying chromatin environment as observed in PBRM1-deficient models. However, Mps1 inhibitor sensitivity in ARID1A-deficient cells has not been widely explored, and the vulnerability may therefore only be present in specific contexts which are, as yet, unknown. It would also be important to interrogate the role of the shared ATPase subunit, SMARCA4, in the maintenance of centromere stability, as SMARCA4 loss, in fact, increased tolerance to Mps1 inhibitors in the cancer cell line HCT116 [50].

In a panel of 375 cancer cell lines from the Cancer Cell Line Encyclopedia (CCLE) [51], PBRM1 protein abundance was positively correlated with the abundance of centromere-associated proteins, suggesting this tend to be a conserved function of PBRM1 across cell and tissue types (figure 3) [48]. This correlation was even stronger when comparing the abundance of centromere-associated proteins with ARID2 abundance (figure 3a), possibly because this subunit acts as a structural scaffold within the PBAF complex, leading to more dramatic perturbation of PBAF when this is lost versus loss of PBRM1 alone [52]. In further agreement with the role of PBRM1 and the PBAF complex in centromere maintenance, a recent study of CIN signatures in a large cohort of tumours found that PBRM1 mutations were associated with a pattern of whole-arm or chromosome changes, proposed to be caused by defective mitoses, rather than being associated with CIN signatures linked to replication stress or DNA repair defects [26]. This association was also seen with another SWI/SNF subunit common to all complexes, ACTL6A, but not with the BAF-specific subunit ARID1A [26]. Consistent with this, the correlation between protein abundance of ARID1A and centromere-associated proteins is less compelling than that of PBAF subunits (figure 3a,c). These data combined provide evidence that a significant contribution of PBRM1 and the PBAF complex to tumour suppression may be in its role maintaining a stable centromere structure, thereby enabling error-free mitoses and stable karyotypes through cell division (figure 3d). Interestingly, the correlation between PBAF and centromere-related protein abundances was even stronger when focusing solely on pericentromere-associated proteins (figure 3b,c), suggesting a particular impact of PBAF on pericentromeres (figure 3d).

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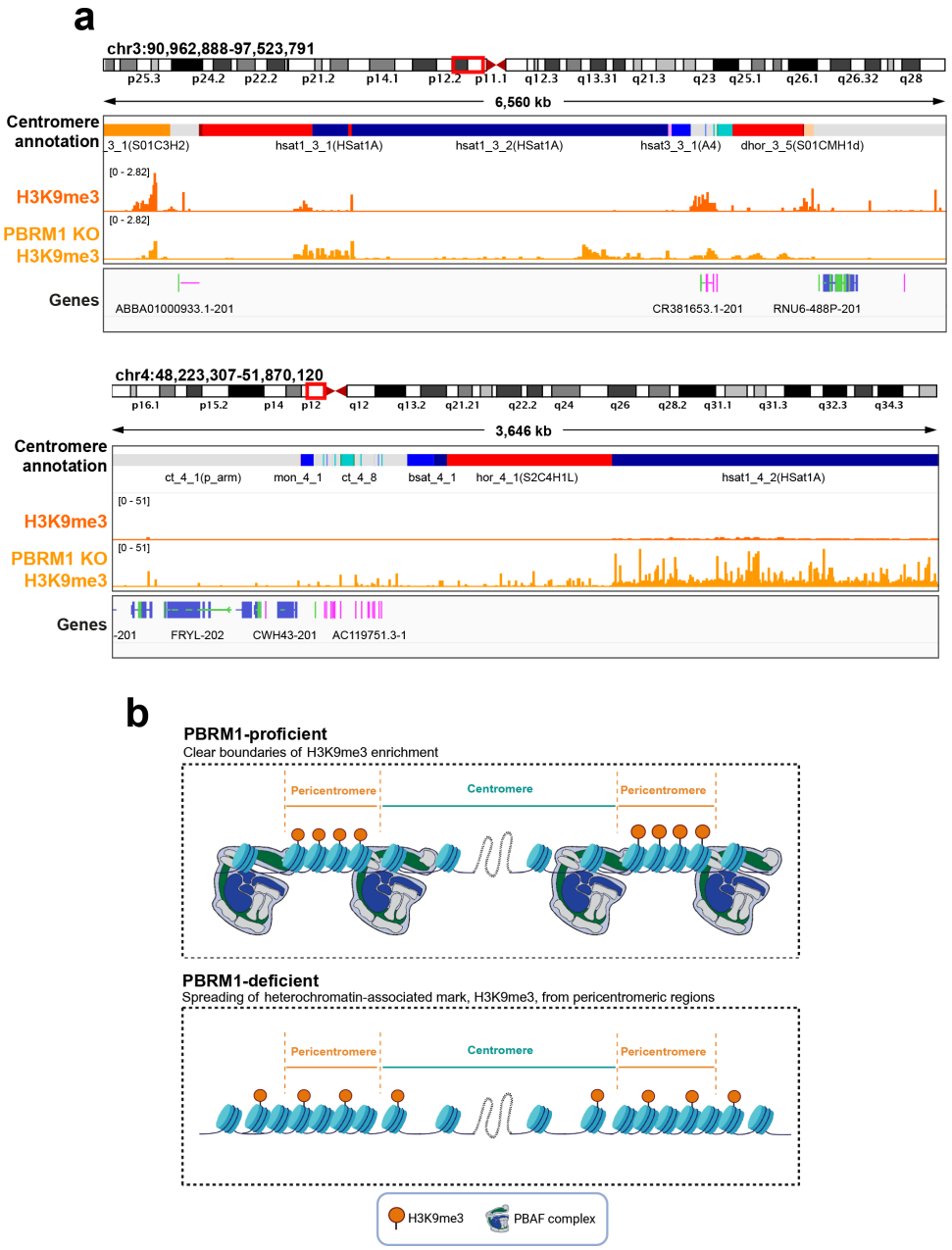


Figure 4. PBRM1-deficient RPE1 cells display an altered pattern of H3K9me distribution and SWI/SNF mapping. (a) Two examples of representative genome tracks displaying mapping locations of enriched *k*-mers across the centromere and pericentromere from analysis of H3K9me3 in parental RPE1 cells (H3K9me3, dark orange), and H3K9me3 in PBRM1 KO RPE1 cells (PBRM1 KO H3K9me3, light orange). Genomic location is indicated at the top, centromeric annotation is shown above the tracks and transcript annotation is shown below. Data in this figure are analysed as described in [48] and are accessible from GSE235294. (b) Schematic summarizing the spreading of H3K9me3 in PBRM1-deficient cells. Created in BioRender.

4. Heterochromatin at pericentromeres

Heterochromatin, which can be divided into facultative or constitutive forms, is associated with a closed chromatin environment and transcriptional repression, in contrast to euchromatin, which is associated with an open chromatin environment and active transcription. Facultative heterochromatin acts to prevent gene expression in a tissue-specific manner and is characterized by histone H3K27me3 and H2AK119ub. Constitutive heterochromatin occurs at sites of repetitive DNA, such as pericentric satellite repeats, and is characterized by the presence of histone H3K9me3, H3K9me2 and H4K20me3 [53,54]. H3K9me3 recruits heterochromatin protein 1 (HP1), which has three forms, HP1α (CBX5), HP1β (CBX1) and HP1γ (CBX3) [55,56]. Interaction of HP1 with the H3K9me3 methyltransferases SUV39H1 and SUV39H2 stimulates further spread of heterochromatin. There is a fine balance required between compartments of open and inactive chromatin, and this balance is regulated by multiple factors, including cohesin turnover and the Mediator–CDK complex, which both limit the spread of heterochromatin [57,58].

As described above, PHC is defined by regions of H3K9me3-containing, transcriptionally repressive heterochromatin. These methylation marks are key for maintaining tight centromeric boundaries, with H3K9me3 maintaining the separation between the flanking pericentric heterochromatic regions and the active centromeric region of the HOR [59], while H3K9me2 also appears to have a role in maintaining a boundary between pericentric and other regions of constitutive heterochromatin [60].

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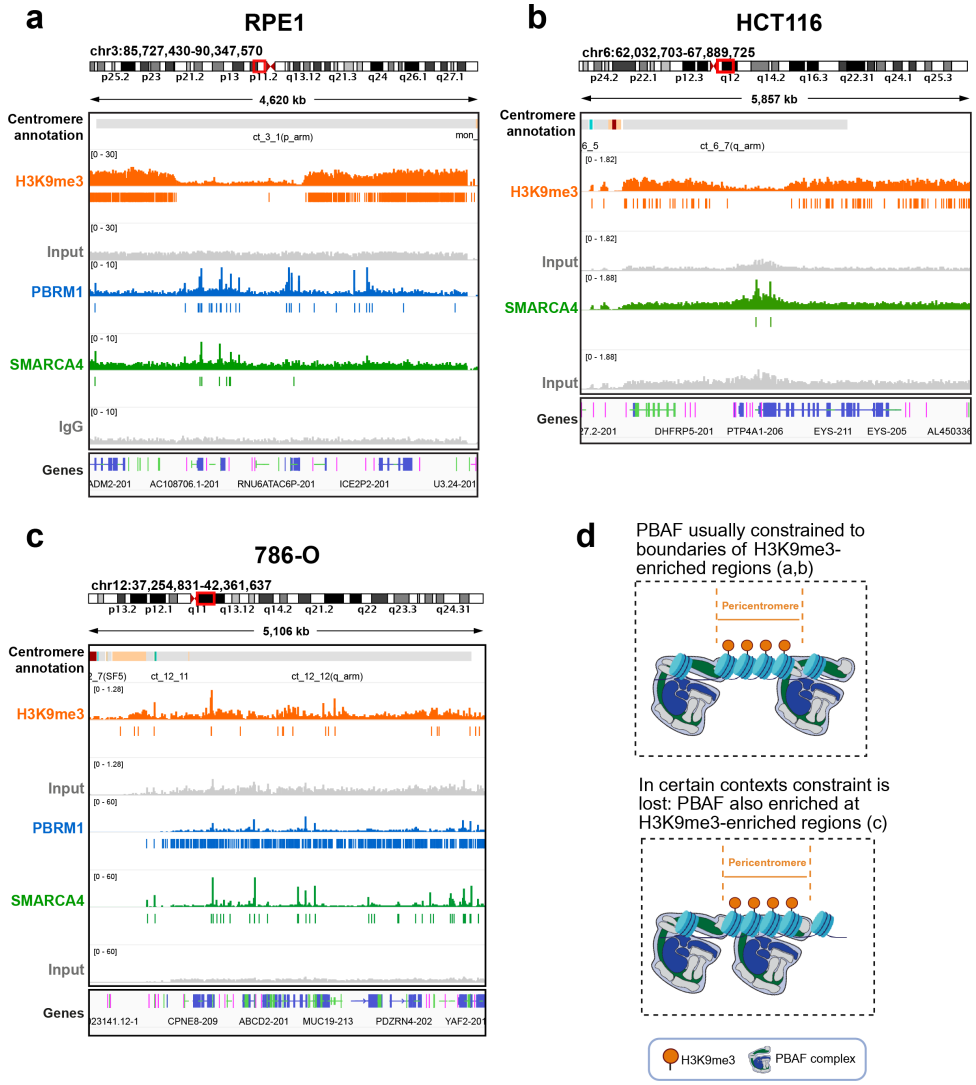


Figure 5. PBAF subunit binding to the pericentric heterochromatin boundary across cell lines. (a–c) Representative genome tracks displaying coverage of uniquely mapping reads from PBRM1 (blue), SMARCA4 (green), heterochromatin marks (H3K9me3 and H4K20me3, orange) and input or IgG controls (grey) in either (a) RPE1 cells (data accessed from GSE235294 [48] and GSE175752 [68]), (b) HCT116 cells (GSE71510 (specific SRA accessions used: SRR2133615, SRR2133616, SRR2133624) [69] and GSE143653 (specific SRA accessions used: SRR10887099, SRR10887219) [70]) or (c) 786-O (data accessed from GSE152681 (specific SRA accessions used: SRR12036678, SRR23588908, SRR12036684, SRR23588912, SRR12036698) [71] and GSE143653 (specific SRA accessions used: SRR10887137, SRR10887193, SRR10887257) [70]). For RPE1 SWI/SNF CUT&RUN (a) mapping, one representative independent biological replicate is shown, with boxes underneath representing peaks that were called as significantly enriched ($q < 0.01$) in at least two out of the three replicates versus their IgG control. For RPE1 histone mark ChIP-seq mapping (a), FASTQ files across the cell cycle were merged for downstream analysis, and one representative independent biological replicate is shown, with boxes underneath representing peaks that were called as significantly enriched ($q < 0.01$) in both replicates versus their input control. For HCT116 (b) and 786-O (c) ChIP-seq datasets, only one biological replicate was available for analysis, and boxes underneath represent peaks that were called as significantly enriched ($q < 0.01$) versus their input control. Data in this figure are analysed as described in [48] and are accessible from GEO databases as indicated in parentheses above. (d) Schematic representing the constraint of PBAF to the boundaries of H3K9me3-enriched regions of pericentric heterochromatin, which can be lost in certain contexts. Created in BioRender.

Numerous studies, including ones using synthetic human artificial chromosomes and neocentromeres, have demonstrated the importance of the balance between the centromeric core domain and the pericentromeric heterochromatin domain for stability of the centromere and for kinetochore attachment, with defects in either transcription or epigenetic marks affecting chromosome segregation and mitotic progression [34,61–65]. Disruption of heterochromatin, through either increasing or decreasing H3K9 methylation levels, has been shown to be clinically important in cancer, particularly acute myeloid leukaemia, and inhibitors targeting the main regulatory proteins are being investigated [66,67].

5. PBAF binding at pericentromeric heterochromatin

In our recent study, we found that the PBAF complex is localized to sites in the pericentromere, and to a lesser extent, the centromere [48]. PBRM1 shows a preference for binding locations in pericentromere that are anti-correlated with H3K9me3 enrichment, and it is particularly associated with boundaries between H3K9me3- and H3K9me2-enriched chromatin (figures 4 and 5) [48]. PBRM1 loss leads to changes in SWI/SNF binding patterns in pericentric regions, suggesting that this subunit is a key determinant of localization [48]. This raises the question of how PBAF is recruited to these sites.

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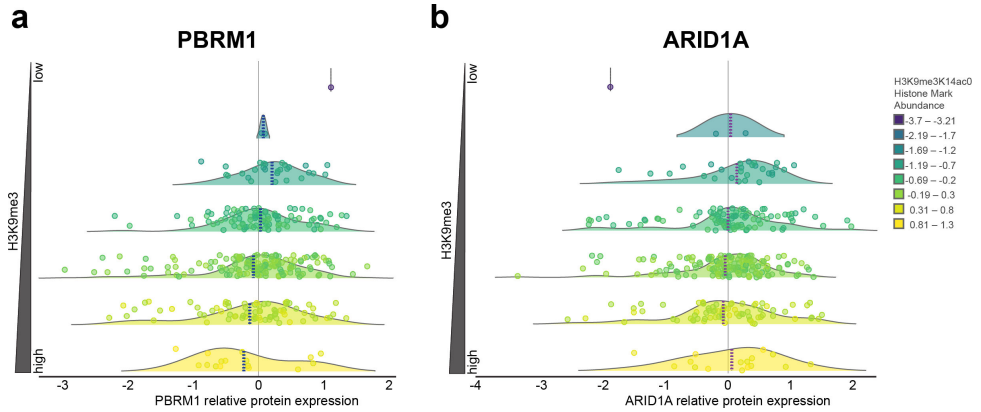


Figure 6. PBRM1 protein levels show an association with H3K9me3 levels across cancer backgrounds. H3K9me3K14ac0 histone mark abundance levels are grouped into bins and colour coded, with a triangle indicating low to high abundance, and plotted against (a) PBRM1 relative protein expression or (b) ARID1A relative protein expression, for cancer cell lines in the CCLE database. Data were accessed and downloaded from DepMap (https://depmap.org/portal—DepMap, Broad (2024). DepMap 24Q4 Public. Figshare+. Dataset https://doi.org/10.25452/figshare.plus.27993248.v1).

One possibility is that the complex is recruited through interaction between PBRM1 and modified histones. PBRM1 (also known as Polybromo-1) is named after its six bromodomains, which can bind acetylated histones, such as H3K14ac [72,73]. The bromo adjacent homology (BAH) domain in PBRM1 can bind to unmodified histone tails of histone H3 and H4 and shows similar levels of binding to both unmodified and H3K9me3 modified tails, but reduced binding to H3K27me3 or polyacetylated histone tails [74,75]. While the specific domains of PBRM1 required for pericentric localization are not yet known, the pattern of modifications in the nucleosomes at particular pericentromeric locations might create a PBRM1 landing pad.

In addition to such a landing pad, interactions with neighbouring heterochromatin components might add to the binding preference for boundaries between H3K9me3- and H3K9me2-containing chromatin regions. It has recently been shown that TNRC18, a chromatin regulator, is an H3K9me3 reader through its BAH domain. Interestingly, a study using BioID proximity labelling revealed an interaction between TNRC18 and SMARCC2, a core SWI/SNF subunit [76]. In addition, interactions between SWI/SNF subunits and HP1 isoforms have been reported [77–79]. Specifically, SMARCA4, the catalytic subunit of SWI/SNF, interacts with HP1 isoforms and has an antagonistic relationship, where it supports HP1 binding, but this in turn represses chromatin remodelling [78]. The other SWI/SNF catalytic subunit, SMARCA2, was identified as an HP1β-interacting factor, and SMARCD1, another core subunit of SWI/SNF, was found associated with the methyltransferase SUV39H1 [79]. PBAF recruitment might therefore be promoted by an interaction with factors such as TNRC18, HP1 and SUV39H1, which are bound directly to neighbouring heterochromatic marks.

6. Impact of PBAF loss on pericentric heterochromatin patterns

We found a small increase in global H3K9me3 by immunofluorescence in PBRM1 knockout cells compared to parental RPE1 cells. Interestingly, this seemed to reflect the fact that the H3K9me3 signal extended a further away from centromeric CENP-A foci. H3K9me mapping in PBRM1-deficient and PBRM1-proficient cell line models was carried out using two different analysis methods—uniquely mapping reads and *k*-mer analysis—to more accurately determine the locations of H3K9me marks [48]. In the absence of PBRM1, there was a shift in both H3K9me2 and H3K9me3 enrichment from the transition arms of the pericentromere towards the HOR. Notably, spreading of H3K9me3 enrichment was apparent in the absence of PBRM1, suggesting the possibility of heterochromatin spreading and altered centromere compartment composition (figure 4) [48].

How might PBAF influence the pattern of chromatin marks in centromeres and pericentromeres? Interestingly, immunoprecipitation experiments of H3K9me3-specific demethylases KDM4A, KDM4B and KDM4C identified SMARCA4 associated with all three as well as an interaction between PBRM1 and both KDM4A and KDM4B [80]. Histone deacetylases (HDACs), such as SIRT6, also play a role in regulating heterochromatin. SIRT6 has specifically been shown to interact with multiple SWI/SNF subunits, including PBRM1 and SMARCA4 [81]. Synthetic lethal interactions have also been discovered between HDAC6 and PBRM1, and HDAC2 and SMARCA4, which could indicate that further dysregulation of the heterochromatin environment is not tolerated by cells [82]. It is possible that PBRM1 recruits histone demethylases and/or deacetylases to prevent the spreading of heterochromatin, and when PBRM1 is lost, this barrier to spreading is weakened (figure 4b).

In support of this possibility, a recent study in fission yeast demonstrated that silencing the homologues of SMARCA4 and PBRM1 (*snf22* and *rsc1*) reestablished the spread of heterochromatin in an HDAC (*clr3*)-deficient background, whereas directly targeting SWI/SNF to these regions disrupted heterochromatin [83]. Also consistent with this possibility, loss of SMARCA4 in lung adenocarcinoma cell models was found to lead to an increase in the number and intensity of H3K9me3 and HP1β foci [84,85]. Finally, PBAF recruitment to centromeres was also identified in the context of meiotic cell division, and loss of the PBAF-specific ARID2 subunit led to alterations in centromeric H2AT120P patterns as well as chromosome passenger complex localization [86].

While SMARCA4-binding patterns in HCT116 cells show patterns of anti-correlation with H3K9me3 enrichment (figure 5a,b) similar to what is observed in RPE1 cells, SWI/SNF subunits mapped in 786-O cells [70,71] do not show such a clear

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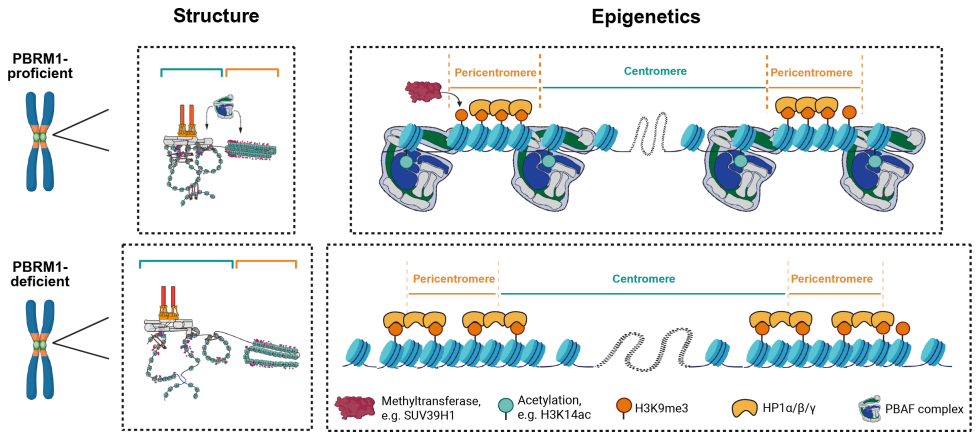


Figure 7. A proposed role of the PBAF complex in constraining heterochromatin at the pericentromere. Model showing the proposed role of PBRM1-containing PBAF complexes at both a structural and epigenetic level, in constraining heterochromatin at the pericentromere, which is affected when PBRM1 is lost. Created in BioRender.

pattern, with SWI/SNF binding also apparent at sites of H3K9me3 enrichment (figure 5c). This could imply that PBAF binding to H3K9me3-enriched chromatin is usually constrained to the boundary, but that in certain cancer contexts, this constraint is lost (figure 5d).

7. Differences between BAF and PBAF and their interplay with heterochromatin

As described above, cells lacking the ARID1A subunit of BAF show sensitivity to mitotic checkpoint perturbation, and mapping data suggest that SWI/SNF association with pericentromeres is not exclusively dependent on PBRM1 (figures 2 and 4) [48]. However, unlike PBRM1-deficient cells, there is no impact on centromere fragility or strong correlation with centromere-associated protein levels (figure 3) [48]. These observations suggest a separate, non-redundant role for BAF at centromeres or pericentromeres.

While PBRM1 was found associated with KDM4A and KDM4B, ARID1B, a BAF-specific subunit, was identified in KDM4C interactomes instead [80]. KDM3A, another H3K9me3 demethylase, which has been shown to interact with ARID1A, regulates splicing after DNA damage [87] and is involved with removing heterochromatin at stalled replication forks to allow fork restart [88]. This could suggest that while both BAF and PBAF influence heterochromatin patterns, these complexes provide non-redundant and separate roles.

Interestingly, an analysis of H3K9me3 levels in cancer cell lines using publicly available data from DepMap (https://depmap.org/portal—DepMap, Broad (2024). DepMap 24Q4 Public. Figshare+. Dataset https://doi.org/10.25452/figshare.plus.27993248.v1) showed a trend towards a negative association between PBRM1 protein expression levels (detected using mass spectrometry) and H3K9me3 levels (measured via global histone modification profiling; figure 6a). This is consistent with the possibility that PBRM1, as part of PBAF, acts as a barrier to heterochromatin spreading. In contrast, no such relationship is apparent between ARID1A protein expression and H3K9me3 levels (figure 6b).

8. Conclusion

The available data are consistent with a model in which the PBAF remodelling complex binds to the boundaries of H3K9me3-enriched PHC and prevents spreading (figure 7). In the absence of PBRM1, SMARCA4-containing complexes are mislocalized, and H3K9me3 inappropriately accumulates in areas where this mark is not normally enriched. These changes lead to an altered structure that impairs CCAN assembly onto centromeric chromatin and consequently leads to centromere fragility, leaving cells vulnerable to mitotic perturbations.

There are still many interesting unresolved questions about how these proteins function, such as the precise recruitment mechanisms that bring PBAF to specific locations in pericentromeres and centromeres. In addition, it is notable that loss of PBRM1 has relatively little impact on cellular growth under unperturbed conditions in the cell line models used in this study [48], while at the same time unleashing centromere fragility. This combination has clear implications for tumourigenesis by allowing increased genome instability without a concomitant loss of fitness. Finally, it would be interesting to determine whether SWI/SNF complex dysregulation influences the stability or evolution of centromeres.

Ethics. This work did not require ethical approval from a human subject or animal welfare committee.
Data accessibility. Datasets analysed in this article have been published elsewhere and are available in publicly available repositories. Accession codes relevant to each analysis are listed in the figure captions.
Declaration of AI use. This article has no additional data.
Authors' contributions. K.A.L.: conceptualization, data curation, formal analysis, writing—original draft, writing—review and editing; A.H.: conceptualization, data curation, formal analysis, writing—original draft, writing—review and editing; J.D.: conceptualization, formal analysis, funding acquisition, writing—original draft, writing—review and editing.
All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

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Conflict of interest declaration. We declare we have no competing interests.
Funding. This work was supported by awards from Cancer Research UK (DRCRPGJun24/100004) and the Medical Research Council (MR/W001276/1).
Acknowledgements. We thank members of the Downs laboratory for helpful discussions.

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