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Graphical Review

The role of the SWI/SNF chromatin remodelling complex in the response to DNA double strand breaks

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ABSTRACT

Mammalian cells possess multiple closely related SWI/SNF chromatin remodelling complexes. These complexes have been implicated in the cellular response to DNA double strand breaks (DSBs). Evidence suggests that SWI/SNF complexes contribute to successful repair via both the homologous recombination and non-homologous end joining pathways. In addition, repressing transcription near DSBs is dependent on SWI/SNF activity. Understanding these roles is important because SWI/SNF complexes are frequently dysregulated in cancer, and DNA DSB repair defects have the potential to be therapeutically exploited. In this graphical review, we summarise what is known about SWI/SNF contribution to DNA DSB responses in mammalian cells and provide an overview of the SWI/SNF-encoding gene alteration spectrum in human cancers.

1. Introduction

Chromatin remodelling complexes can be divided into four families based on the sequence and characteristics of the ATPase subunit: SWI/SNF, CHD, ISW, and INO80 [1]. The SWI/SNF family of remodellers is capable of altering chromatin organisation through sliding nucleosomes or evicting histones from chromatin [1]. In mammalian cells, current data suggest that the SWI/SNF complexes in somatic cells can be divided into three basic categories: BAF (BRG1/BRM Associated Factors), PBAF (Polybromo-associated BAF) and ncBAF or GBAF (non-canonical BAF or GLTSCR1/1L-associated BAF) ([2]; Fig. 1).

There are at least 29 subunits that have been identified as constituents of the various mammalian SWI/SNF complexes (Fig. 1C), but many of these are paralogs and only one of the homologous subunits will be incorporated into a complex (Fig. 1A). For example, complexes contain only one of the three related SMARCD subunits (SMARCD1, SMARCD2 or SMARCD3). Given that many of the genes encoding these subunits also encode multiple isoforms, the combinatorial potential for SWI/SNF complex variations is remarkable.

Recently, an elegant cryo-EM structure of the human BAF complex bound to a nucleosome was reported, revealing the organisation of many of the subunits and providing insights into the mechanism of remodelling [3]. The complex can be divided into three modules: ATPase, ARP, and Base (Fig. 1B). These form a clamp shape that envelopes the nucleosome, with direct contacts made by the ATPase and the conserved SMARCB1 (BAF47) subunits (Fig. 1B). While there will be interesting differences introduced by alternative subunit composition, the conservation of the main players suggests that the overall architecture of the related SWI/SNF complexes will be roughly conserved.

Double strand breaks (DSBs) in DNA are among the most deleterious forms of DNA damage and, if these are mis-repaired or not repaired, can result in genome instability or cell death. Consequently, there is a robust signalling cascade initiated in response to DNA DSBs that can lead to transcriptional upregulation of repair genes, cell cycle arrest, and in some cases, programmed cell death. This signalling cascade is initiated by the apical kinases ATM, ATR and DNA-PK, resulting in the phosphorylation of downstream targets including the histone variant H2AX (for review, see [4]).

Depletion, mutation or loss of SWI/SNF subunits has been shown to lead to sensitivity to DNA DSB inducing agents (for review, see [5,6]). This could, of course, be an indirect consequence of transcriptional misregulation of factors involved in the cellular response to DSBs. In support of a direct role, however, is the finding that SWI/SNF complexes are rapidly recruited to DSBs [7–14]. These results were generated in multiple different cell types and made use of different experimental approaches (microscopy and chromatin immunoprecipitation) and different methods of DNA DSB induction (laser microirradiation, ionising radiation and enzymatically introduced DNA DSBs). These robust data therefore argue for a direct role, but do not exclude the possibility that indirect roles also contribute to DNA DSB responses. The mechanism of recruitment,

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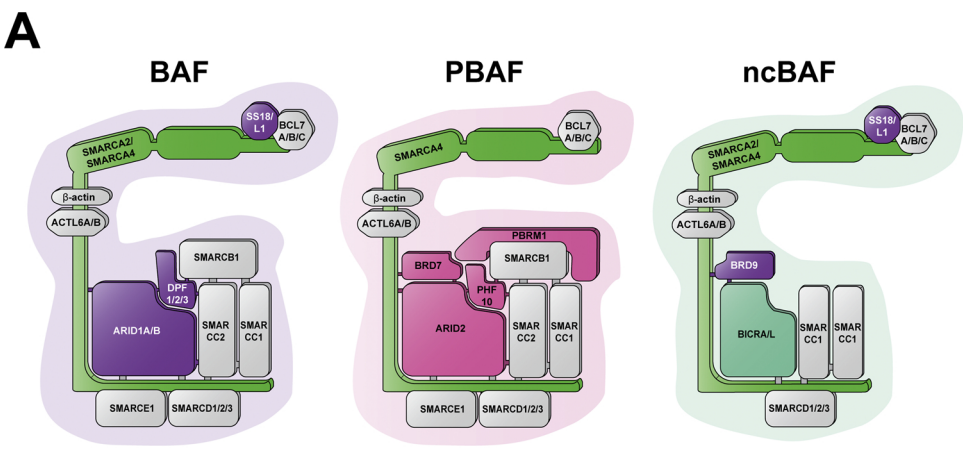

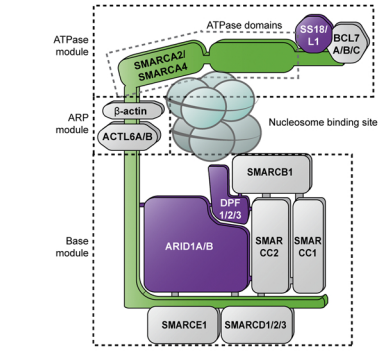

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Name	Alternative name	BAF	PBAF	ncBAF	Location
SMARCA4*	BRG1	✓	✓	✓	chr19p13.2
SMARCC1	BAF155	✓	✓	✓	chr3p21.31
SMARCD1	BAF60A	✓	✓	✓	chr12q13.12
SMARCD2	BAF60B	✓	✓	✓	chr17q23.3
SMARCD3	BAF60C	✓	✓	✓	chr7q36.1
BCL7A	BCL7A	✓	✓	✓	chr12q24.31
BCL7B	BCL7B	✓	✓	✓	chr7q11.23
BCL7C	BCL7C	✓	✓	✓	chr16p11.2
ACTL6A	BAF53A	✓	✓	✓	chr3q26.33
ACTL6B	BAF53B	✓	✓	✓	chr7q22.1
ACTB	β-actin	✓	✓	✓	chr7p22.1
SMARCC2	BAF170	✓	✓		chr12q13.2
SMARCB1	BAF47	✓	✓		chr22q11.23
SMARCE1	BAF57	✓	✓		chr17q21.2
ARID1A	BAF250A	✓			chr1p36.11
ARID1B	BAF250B	✓			chr6q25.3
DPF1	BAF45B	✓			chr19q13.2
DPF2	BAF45C	✓			chr11q13.1
DPF3	BAF45D	✓			chr14q24.2
SMARCA2*	BRM	✓		✓	chr9p24.3
SS18	SSXT	✓		✓	chr18q11.2
SS18L1	CREST	✓		✓	chr20q13.33
ARID2	BAF200		✓		chr12q12
PHF10	BAF45A		✓		chr6q27
PBRM1	BAF180		✓		chr3p21.1
BRD7	BRD7		✓		chr16q12.1
BICRA	GLTSCR1			✓	chr19q13.33
BICRAL	GLTSCR1L			✓	chr6p21.1

Fig. 1. Structure and subunit composition of the mammalian SWI/SNF chromatin remodelling complexes. **A**. There are three major SWI/SNF complexes, defined by subunit composition; BAF, PBAF and ncBAF. Each contains a catalytic subunit (green), core subunits (grey), and complex-specific subunits (purple for BAF, pink for PBAF, or teal for ncBAF). Where one of a family of paralogues is present in a complex, the subunit is labelled with all (e.g. DPF1/2/3 to indicate DPF1, DPF2, or DPF3). **B**. The subunit organisation of BAF in complex with a nucleosome determined by cryo-EM [3]. The complex is divided into three modules: ATPase, ARP and Base. **C**. Table of SWI/SNF subunits. Commonly used alternative names are provided. Ticks indicate which of the SWI/SNF complexes contain the subunit. The chromosomal location of each gene is indicated in the final column.

however, is still unclear, with a number of different factors implicated, such as BRIT1 [11], and E2F working together with RB [10] (Fig. 2). In addition, histone modifications play a role, with evidence that p300/CBP dependent H3 and H4 acetylation as well as LKB1/AMPK2-dependent H2B phosphorylation contribute to SWI/SNF recruitment [12–15]. Interestingly, it was recently found that E2F recruits the histone acetyltransferases p300 and CBP to DNA DSBs [16], raising the possibility that E2F/Rb and p300/CBP represent a single recruitment pathway. However, it's also possible and indeed likely that the SWI/SNF complexes have multiple recruitment mechanisms, and their use could depend on the location of the DNA DSB, the cell cycle phase, or the cell type. In addition, different SWI/SNF complexes are most likely targeted through distinct pathways, and further work is needed to fully understand DSB recruitment mechanisms.

Following the detection and signalling of DNA DSBs, there are two major pathways for DSB repair in mammalian cells; non-homologous end joining (NHEJ) and homologous recombination (HR; [4]). SWI/SNF complexes have been implicated in both of these pathways (described below) as well as other cellular pathways that impact on genome stability [5,6]. There are additional DNA DSB repair pathways, such as alternative end joining (alt-EJ [4];), which become particularly important when there are defects in either NHEJ or HR, but currently, there is only limited evidence regarding SWI/SNF functions in these other pathways [17] so this will not be covered further.

The first step of NHEJ involves the Ku heterodimer (Ku70 and Ku80) binding to the broken DNA ends (Fig. 3A). Subsequently, additional repair factors, including DNA-PKcs, XRCC4 and Ligase 4, associate with the DSB and facilitate repair. In some cases, depending on the nature of the break, end processing is required prior to ligation (for review, see [4]). Subunits of the BAF complex (including ARID1A and SMARCA2), but not PBAF subunits (such as SMARCA4), are required for efficient NHEJ using a reporter construct [12,14]. This appears to function by promoting the association of Ku with the DSB [12,14]. At its simplest, this could suggest that BAF is required to re-organise chromatin flanking the DNA DSB in order to allow repair factors to bind and there is evidence to support this [17]. However, it is possible that BAF and/or PBAF have additional downstream functions during NHEJ.

During HR, the broken DNA ends need to be resected and the ssDNA coated with RPA, which is then replaced with RAD51. Following RAD51 filament formation, the sister chromatid is used as a template for repair (Fig. 3B; for review, see [4]). There is a clear consensus that HR (generally measured with the use of a reporter system) does not function effectively in cells lacking SWI/SNF subunits [8–11,18] and that the formation of RAD51 foci is impaired [8,9,11,19], implicating SWI/SNF in steps upstream of this event (Fig. 3B). Notably, these studies investigated subunits from both BAF and PBAF, but it is not yet clear whether these function redundantly at the same lesions in the same cell types, or make more specialised contributions.

Given the need during HR for manipulation of both the chromatin flanking the DSB and the sister chromatid during strand invasion, a requirement for chromatin remodelling complexes is not surprising. Indeed, many chromatin remodellers have been implicated in HR, particularly with regard to resection. There is evidence that SWI/SNF contributes to the ability of cells to generate single stranded DNA [10,11,20], but also contradictory evidence that it doesn't [8]. Moreover, while it is very likely that the chromatin remodelling activity of SWI/SNF complexes is important for DNA DSB repair and there is evidence to support this [7,17,18], overexpression of a catalytically inactive form of SMARCA4 (BRG1) did not impair HR activity measured by a reporter assay [21], raising the possibility that SWI/SNF complexes can also contribute to HR activity through other mechanisms, such as scaffolding or recruitment

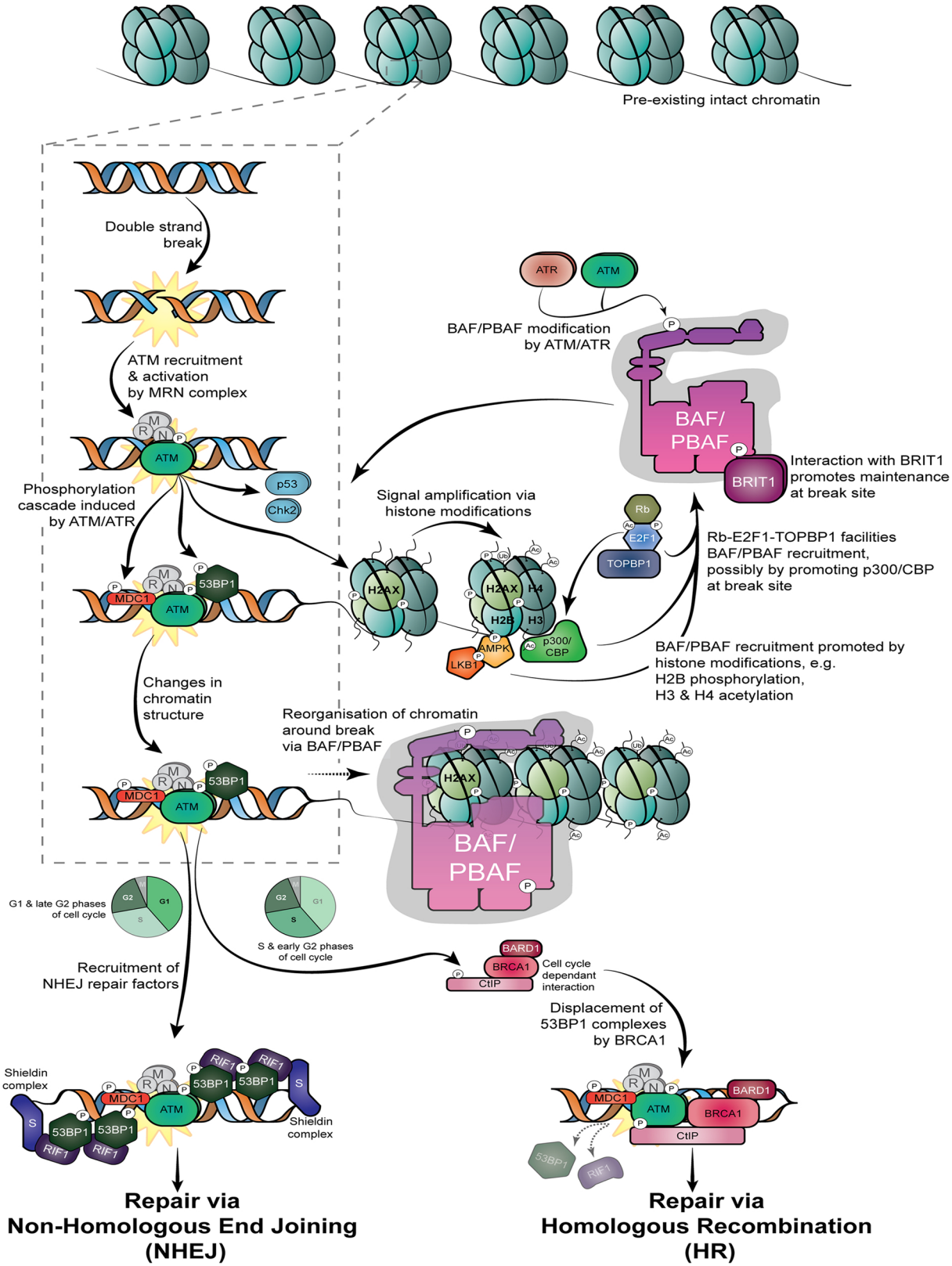

Fig. 2. The SWI/SNF complexes are recruited early to DNA DSBs. Pre-existing chromatin structure (top) will influence pathway choice and cellular responses to the DNA DSB (for review, see [26]). Following DNA DSB induction, ATM is recruited by the MRN complex and initiates a signal transduction cascade (for review, see [4]). Evidence suggests that BAF and PBAF recruitment is an early event and is facilitated by TOPBP1/E2F/RB (*10*), p300/CBP-dependent histone acetylation [12,15], LKB1/AMPK-dependent histone phosphorylation [13] and BRIT1 [11]. Subunits of both BAF and PBAF are targets of ATM and ATR-dependent phosphorylation [5,6]. It is likely that not all recruitment mechanisms are used at all DNA DSBs or with all SWI/SNF complexes. The SWI/SNF complexes contribute to reorganisation of chromatin flanking the DNA DSB. It is not yet clear how much SWI/SNF-dependent chromatin reorganisation impacts on the signalling events that influence DNA DSB repair pathway choice (bottom).

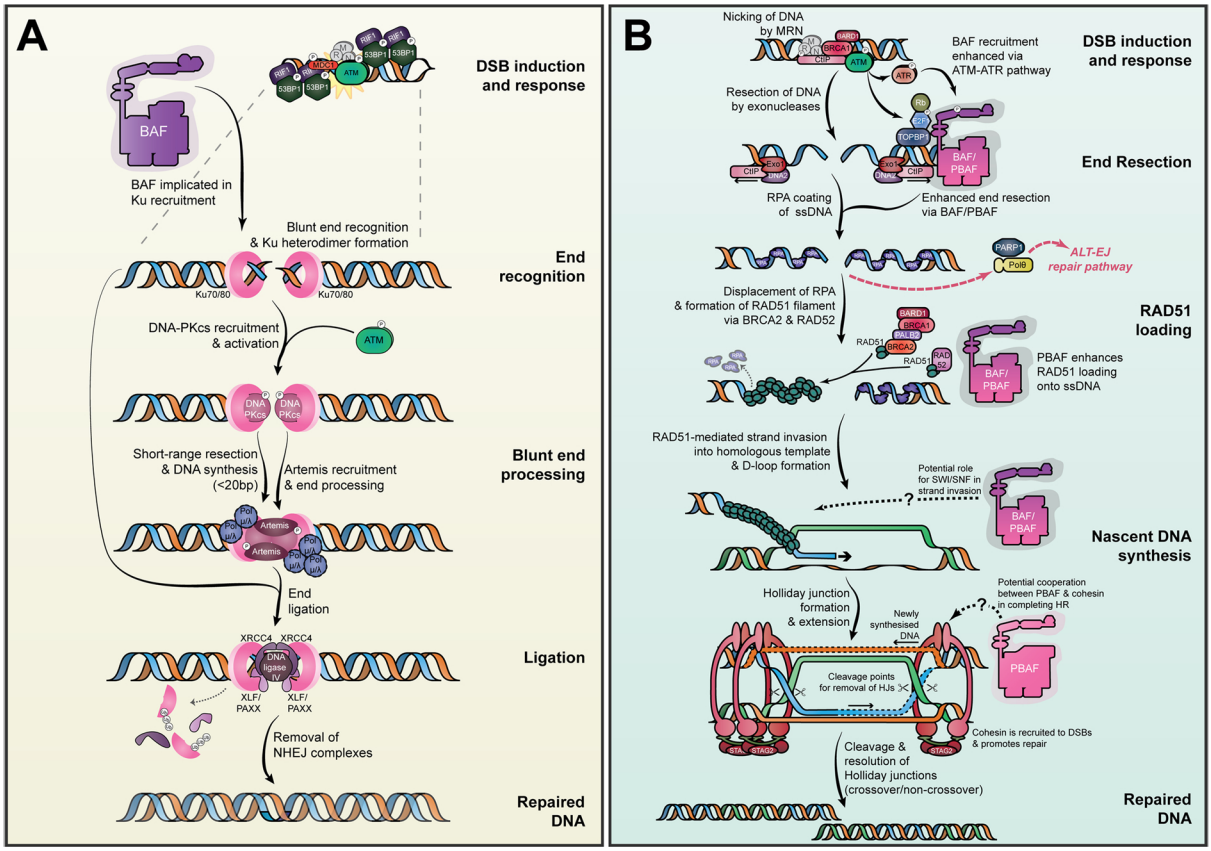

Fig. 3. The role of SWI/SNF complexes in NHEJ (A) and HR (B). **A.** NHEJ is initiated by Ku heterodimer binding to the DNA ends, followed by processing, ligation, and removal of the repair proteins (for review, see [4]). Consistent with early recruitment to the DSB (Fig. 2), BAF activity has been shown to promote Ku heterodimer association with the broken DNA ends [12,14]. Downstream steps (such as XRCC4 recruitment and NHEJ-mediated repair) are therefore also impaired when BAF is dysfunctional [12,14], but it is possible that SWI/SNF has additional functions in this pathway. **B.** HR is initiated with end resection, mediated by exonucleases such as CtIP, Exo1 and DNA2, resulting in RPA bound ssDNA. Next, RPA is replaced with RAD51 filaments. RAD51-coated ssDNA invades the template (strand invasion) followed by holiday junction formation and resolution (for review, see [4]). BAF and PBAF promote efficient resection [10,11,20] and consequently RAD51 foci formation, but may also separately facilitate RAD51 loading [8]. SWI/SNF complexes may also function at later steps through promoting sister chromatid cohesion at the DNA DSB [23] and/or through coordination of the generation and use of RNA molecules used during repair.

functions (Fig. 3B). Finally, PBAF has been shown to promote sister chromatid cohesion and to work with cohesin at DNA DSBs [21,23], and therefore might contribute to HR through this activity (Fig. 3B).

RNA polymerase II-mediated transcription is repressed when a DNA DSB occurs in chromatin nearby (for review see [24], Fig. 4). Failure to do this results in impaired DNA DSB repair, and evidence suggests that both NHEJ and HR can be affected [24]. We found that the PBAF complex is required for efficient transcriptional repression in response to DNA DSBs [7,22]. PBAF functions downstream of ATM, and ATM-dependent phosphorylation of the PBRM1 (BAF180) subunit is required for efficient repression at DNA DSBs. Of note, the catalytic activity of SMARCA4 (BRG1) is also required, suggesting that chromatin remodelling contributes to the repression of RNA pol II mediated transcription. Multiple other chromatin modifying activities have also been implicated in this activity ([24], Fig. 4), and it will be important to determine the relationship between these factors.

It is worth noting that RNA species play an important role in promoting the repair of DNA DSBs [25]. Repair of DSBs in transcribed regions preferentially depends on HR, and recent evidence suggests RNA molecules contribute to repair in these areas [26]. The repression of transcription in chromatin flanking DNA DSBs must therefore be coordinated with the production and use of RNA molecules that are needed to promote repair. It is reasonable to speculate that SWI/SNF contributes to the coordination of these events at DSBs through its chromatin remodelling activities.

Overall, the evidence demonstrates that SWI/SNF complexes are recruited to DNA DSBs and contribute to DNA DSB repair through chromatin reorganisation. The defects caused by deficiency in SWI/SNF complexes are not as severe as loss of DNA damage signalling and core repair proteins, indicating that this is not a central component of DNA DSB repair. Instead, it appears that there are multiple steps that are facilitated by SWI/SNF activity, which makes elucidating the precise mechanisms by which it functions challenging. Moreover, a major outstanding question in the field is defining the specialised functions, insomuch as they exist, of the different SWI/SNF complexes at DNA DSBs.

Notably, genes encoding subunits of the SWI/SNF complexes are frequently altered in cancer (Fig. 5; [27–40]). A great deal of attention has focused on mutations, but notably, amplifications represent a significant proportion of the alterations (Fig. 5A). Interestingly, the genes that are most frequently amplified are distinct from those that are most frequently mutated or deleted (Fig. 5A). Most SWI/SNF mutations are inactivating, consistent with studies that indicate that loss of function of these genes drives tumourigenesis (Fig. 5B; [5,6]). The frequent amplifications (Fig. 5C) could suggest that SWI/SNF upregulation drives tumourigenesis, but more likely reflect SWI/SNF dysfunction due to altered complex composition when normal stoichiometry is disrupted. A greater understanding of the biochemistry and localisation of dysfunctional complexes will help to illuminate the patterns of amplification and mutation or deletion.

The extent to which the functions of SWI/SNF complexes at DNA DSBs contribute to tumourigenesis is still unclear and may vary by both subunit and tissue. Nevertheless, defects in DNA DSB repair responses are common in cancer, which highlights the importance of

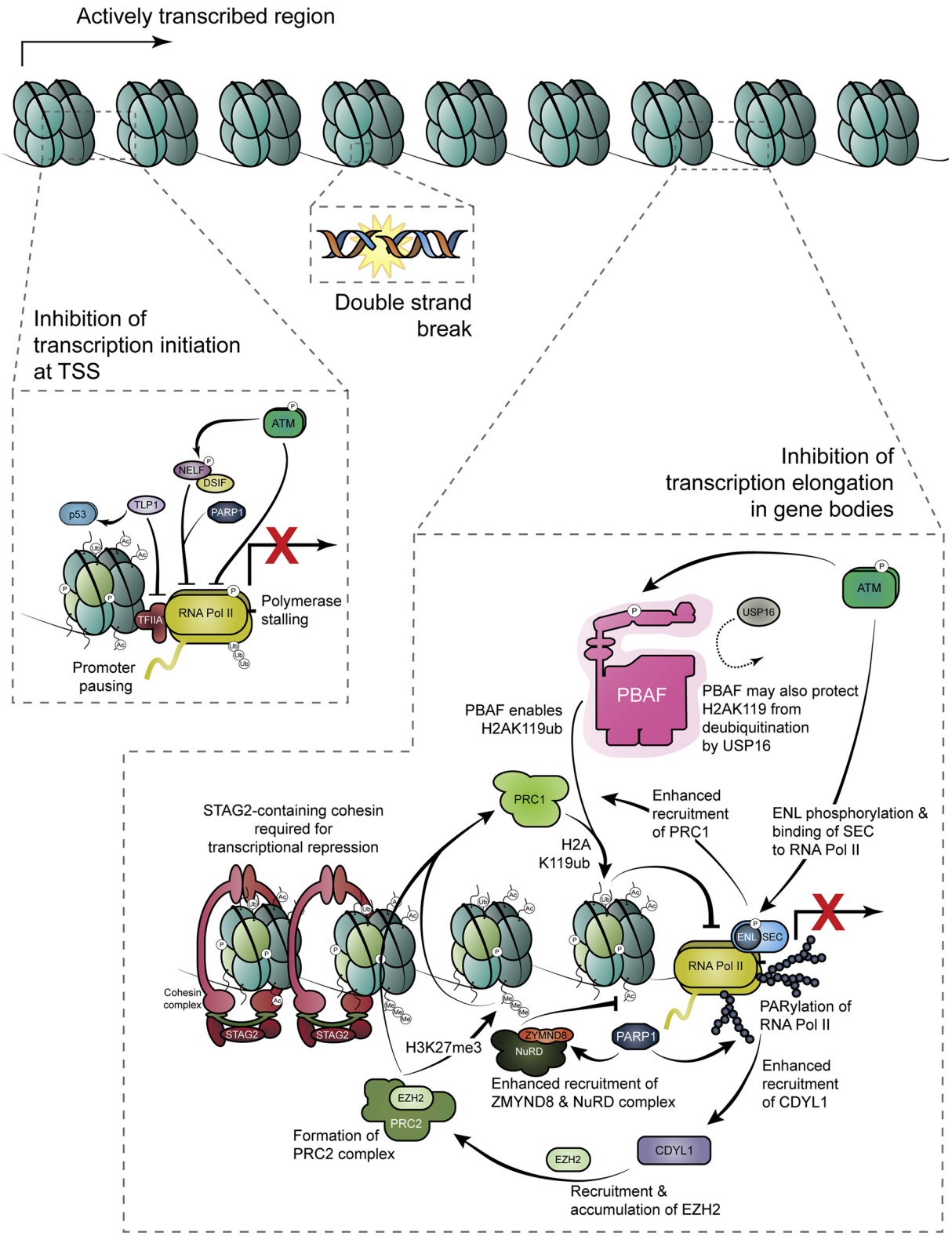

Fig. 4. The PBAF SWI/SNF complex contributes to transcriptional silencing of RNA polymerase II-transcribed genes flanking DNA double strand breaks. In response to a DNA DSB, ongoing transcription in nearby chromatin is repressed. Multiple chromatin modifying factors are involved (for review, see [24]), including the polycomb repressor complexes 1 and 2 (PRC1 and PRC2), leading to H2A K119 ubiquitination in the vicinity of the DNA DSB. PBAF works together with the STAG2-containing cohesin complex to mediate transcriptional repression near DNA DSBs [7,22]. The mechanism by which PBAF mediates this function is not yet clear, but H2A K119 ubiquitination does not accumulate efficiently without PBAF [7,22], indicating that it is upstream of PRC1 and PRC2 functions.

understanding exactly how SWI/SNF complexes are working at DNA DSBs and what consequences arise from their dysregulation. Furthermore, an understanding of exactly how dysregulation, either through loss of function or amplification, of each individual subunit will impact on DNA DSB responses is required.

Evidence is emerging that the defects in genome stability functions

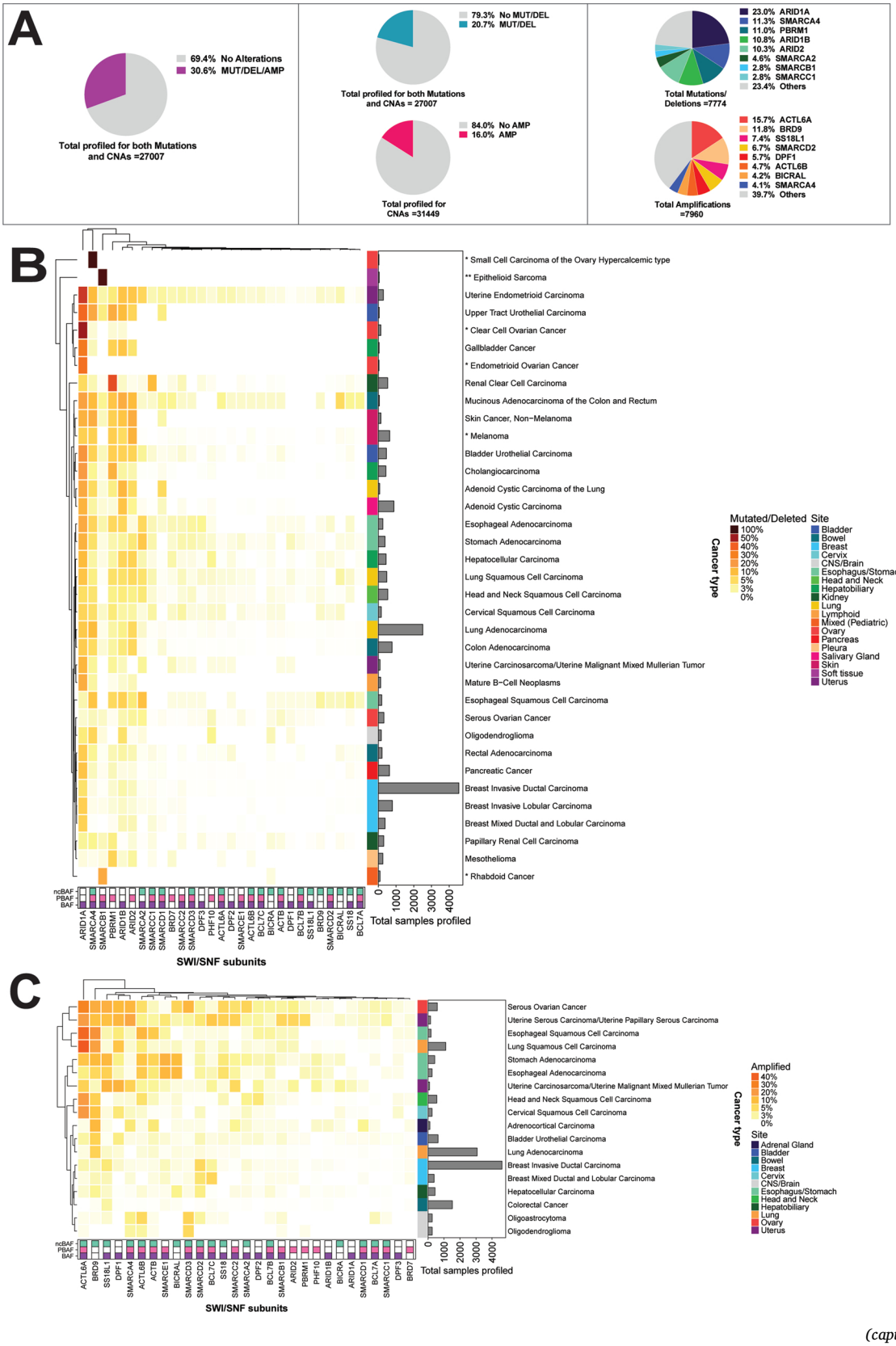

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Fig. 5. Genes encoding subunits of SWI/SNF complexes are frequently mutated or misregulated in cancer. **A.** Left panel: proportion of cancer samples with alterations in one or more SWI/SNF subunits. Middle panel: proportion of cancer samples with mutations or deletions (top) or amplifications (bottom) of SWI/SNF subunits. Right panel: The cancer samples with mutations/deletions (top) or amplifications (bottom) in SWI/SNF subunits are broken down by specific genes. CNA stands for copy number alterations. **B**. Heatmap showing the frequency of mutations or deletions of individual SWI/SNF subunits in the indicated cancer types. The complex(es) membership of each subunit is indicated in teal (ncBAF), pink (PBAF) or purple (BAF) along the lower axis. The total number of samples profiled in each study is indicated in grey. **C**. Heatmap showing the frequency of amplifications of individual SWI/SNF subunits in the indicated cancer types. The complex(es) membership of each subunit is indicated in teal (ncBAF), pink (PBAF) or purple (BAF) along the lower axis. The total number of samples profiled in each study is indicated in grey. Heatmaps were clustered by Euclidean distance. *Mutation data only shown, **Deletion data only shown.
Heatmaps were generated using the r package described in [42] and the data was downloaded from cBioPortal on 16 June 2020. The results published here are based on data from references [27–40], and from data generated by the Therapeutically Applicable Research to Generate Effective Treatments (https://ocg.cancer.gov/programs/target) initiative, phs000218 (the data used for this analysis are available at https://portal.gdc.cancer.gov/projects), and from data generated by the TCGA Research Network (https://www.cancer.gov/tcga). Cancer types shown here were those that had more than 3 % of samples containing SWI/SNF alterations.

that arise as a consequence of SWI/SNF loss lead to therapeutically exploitable vulnerabilities. Cells lacking ARID1A (BAF250A) are sensitive to ATR inhibitors, and in mouse models, tumours lacking ARID1A responded better to treatment with an ATR inhibitor [41]. In addition, PARP inhibitors also lead to greater tumour response in mouse models where ARID1A is deficient [20], and both ATR and PARP inhibitors were identified in a screen for radiosensitizers of ARID1A deficient cells (*17*). Since ARID1A is frequently mutated in cancer (Fig. 5), these findings are clinically important. It will be important to determine whether these sensitivities extend to cells lacking other SWI/SNF subunits. It is also important to understand the mechanistic basis for these relationships, which could relate to the role of SWI/SNF in HR or in replication stress responses. However, as is the case for understanding SWI/SNF biology in all areas, the fact that SWI/SNF complexes have so many potentially relevant and interconnected cellular activities makes this challenging.

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