Defects in DNA damage responses in SWI/SNF mutant cells and their impact on immune responses

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Keywords: SWI/SNF, BAF, PBAF, chromatin remodelling, DNA repair, double-strand break repair, DNA damage, ARID1A, PBRM1, SMARCA4, cGAS/STING, neoantigen, cancer, immunotherapy

ABSTRACT

The mammalian SWI/SNF chromatin remodelling complexes are commonly dysregulated in cancer. These complexes contribute to maintaining genome stability through a variety of pathways. Recent research has highlighted an important interplay between genome instability and immune signalling, and evidence suggests that this interplay can modulate the response to immunotherapy. Here, we review emerging studies where direct evidence of this relationship has been uncovered in SWI/SNF deficient cells. We also highlight genome maintenance activities of SWI/SNF that could potentially shape immune responses and discuss potential therapeutic implications.

1. Introduction

SWI/SNF complexes are a conserved eukaryotic family of chromatin remodelling activities. In mammalian cells, this family can be divided simplistically into three categories: BAF (BRG1/BRM Associated Factors), PBAF (Polybromo-associated BAF), and GBAF (GLTSCR1/1L-associated BAF; also called ncBAF). BAF, PBAF and GBAF share some core subunits (Table 1) and are defined by complex-specific subunits [1]. Of note, many subunits have multiple isoforms and paralogues. Moreover, each complex will have one of two catalytic subunits; SMARCA4 (also called BRG1) or SMARCA2 (also called BRM). Each category of SWI/SNF complex (BAF, PBAF and GBAF) therefore has many possible variations, and a full understanding of the specific functions of each is not yet known.

The SWI/SNF complexes regulate gene expression through remodelling activity at promoter and enhancer elements [2]. Misregulation of gene expression in cells with SWI/SNF deficiency can contribute to changes in genome stability, but SWI/SNF complexes also play a transcription-independent role in maintaining genome stability (described in more detail below). For example, SWI/SNF complexes are recruited to sites of DNA double strand breaks and promote their timely and accurate repair (for review, see [1]).

It has become increasingly apparent that genome instability can feed into both innate and adaptive immune responses (for recent reviews on this topic, see Zhou and Mouw, Ha et al, Uchihara and Shibata, and Zierhut, this issue). Genome instability events, such as mitotic progression with unrepaired DNA damage, that lead to the generation of cytosolic DNA fragments can activate the cGAS/STING pathway, triggering a type I interferon response. Furthermore, defective mismatch repair or misrepair of DNA breaks that culminate in elevated tumour mutational burden (TMB) can result in neoantigen formation. Moreover, DNA damage leads to enhanced HLA class I presentation [3]. Each of these responses has the potential to turn an immunologically ‘cold’ tumour into a ‘hot’ one, which in turn can improve the response to immune checkpoint inhibitor (ICI) therapy [4].

Interestingly, SWI/SNF alterations have been identified as prognostic indicators for ICI therapy response. Specifically, loss of function mutations in PBRM1 subunit correlate with improved response to ICI therapy [5-9]. In addition, mutations in other subunits, including ARID1A and ARID2, also showed potential prognostic value [10, 11]. However, relationships were not apparent in all tissue types or with all SWI/SNF subunits, and in some cases, no positive association between SWI/SNF alterations and response to ICI therapy was apparent (for example, [12-15]). Understanding how SWI/SNF deficiency impacts on immune responses, and consequently how SWI/SNF deficiency might influence ICI therapy response, is still an open and clinically important question.

There is evidence that SWI/SNF complexes can regulate expression of genes involved in immune signalling (for example, [9, 16, 17]), and therefore altered SWI/SNF activity could influence ICI therapy response through the resulting changes in immune gene expression. However, here, we focus on SWI/SNF activities involved in genome maintenance that might influence immune responses indirectly. In some cases, there is direct evidence of a relationship between genome instability caused by SWI/SNF deficiency and immune signalling. In addition, we highlight areas where the impact of specific SWI/SNF-dependent

DNA damage responses on immune responses is predicted but has yet to be tested. Given the prevalence of SWI/SNF dysregulation in cancer, understanding these relationships in more detail will be helpful when considering therapeutic approaches.

2. ARID1A, mismatch repair, and neoantigen formation

ARID1A is a defining subunit of the BAF complexes (Table 1) and, of all the SWI/SNF subunits, is the most frequently mutated in cancer [1]. ARID1A deficiency is associated with impaired mismatch repair (MMR) in multiple cancers, including colon [18].

MMR is initiated by a heterodimer made up of MSH2 together with either MSH6 (to form MutSα) or MSH3 (to form MutSβ) [19]. Recently, a proteomic analysis of ARID1A interacting proteins identified MSH2 ([20]; Fig. 1A), suggesting that ARID1A might promote MMR by recruiting MSH2 to chromatin. Alternatively, ARID1A-dependent chromatin remodelling when interacting with MMR proteins could facilitate MutSα/β sliding and lesion processing, particularly in dealing with lesions in proximity to nucleosomes. Both mechanisms would lead to improved MMR efficiency, and consistent with this, ARID1A deficient cells showed impaired MMR activity using a reporter assay [20].

MutSα and MutSβ form a clamp on DNA and respond to different structures. Specifically, MutSα binds to mispaired DNA or short insertion/deletion loops where MutSβ binds larger loops in DNA [19]. Surprisingly, neither MSH6 nor MSH3 was identified in the ARID1A interactome, so it will be of interest to determine how these interactions are regulated and whether both MutSα and MutSβ are influenced by ARID1A. Furthermore, MMR proteins function in other repair pathways [21], and the ARID1A interaction with MSH2 might play a role here as well.

Increased TMB resulting from defective MMR can influence the tumour microenvironment, and this is thought to be a result of increased neoantigen formation [22]. In mouse models, ARID1A-deficient tumours were immunologically hot and responded more favourably to anti-PD-L1 ICI therapy [20], and there is evidence that at least some ARID1A deficient human cancer samples have elevated TMB and respond more favourably to ICI therapy [23, 24].

Whether the ARID1A impact on MMR varies by tissue type and genetic context remains to be determined, and ARID1A loss impacts on DNA repair gene expression in at least some cell types (for example, [25]; Fig. 1B). Moreover, loss of ARID1A is correlated with high PD-L1 expression in gastric cancer [26]. There is evidence that ARID1A-dependent remodelling activity is important for regulating the PD-L1 encoding gene (CD274; [27]), but additionally, evidence that ARID1A is important for PI3K/ATK/mTOR signalling, which influences PD-L1 levels [26]. These mechanisms will influence response to ICI therapy in ARID1A-deficient cancers regardless of MMR activity alterations (Fig. 1B).

3. PBRM1, the G2/M DNA damage checkpoint, and DNA damage inflammatory signalling

PBRM1 is specifically found within the PBAF remodelling complex (Table 1) and is frequently mutated in clear cell renal cancer [1]. We recently found that PBAF is required for the p53-dependent maintenance of the G2/M DNA damage checkpoint [28]. In its absence, cells

progress through mitosis with unrepaired DNA damage. This results in cytosolic DNA and micronuclei formation, which activates the cGAS/STING pathway. Importantly, PBRM1 deficient cells show increased interferon signalling following DNA damaging treatments such as ionising radiation when compared with PBRM1 proficient cells (Fig. 2).

PBRM1 deficiency has been identified in several studies as a predictive biomarker of ICI therapy response (eg [6, 7, 9, 12]), but the predictive value is not perfect. If the role of PBRM1 in preventing DNA damage induced inflammatory signalling is pertinent to the response to ICI therapy, we can expect that patients with PBRM1 deficient cancers will respond best when a) DNA damage is present at levels such that repair is incomplete when cells move through mitosis and b) the cGAS/STING pathway is intact and able to sense the resulting cytosolic DNA (Fig. 2).

We tested the second prediction using clinical trial data in which ICI therapy was used on renal cancer patients. In support of this model, we found that patients with PBRM1 deficient cancers responded well to ICI therapy when cGAS expression was normal, but when low, responses were poor [28]. Treatments that directly induce DNA damage are not commonly used to treat clear cell renal cancer, but these results suggest that this could potentiate the response to ICI therapy in patients with PBRM1-deficient, cGAS-proficient cancers.

4. SWI/SNF deficiency, R loop formation, and DNA damage inflammatory signalling

R loops are nucleic acid structures composed of a DNA:RNA hybrid and the displaced single-stranded DNA, which can form during transcription. BRCA1 prevents the accumulation of R loops, but in its absence, R loops are processed by XPF and XPG and released into the cytosol where they activate the cGAS/STING pathway [29].

Both BAF and PBAF have been implicated in preventing the accumulation of R loops. Cells lacking either the ARID1A subunit of BAF [30, 31] or the PBRM1 subunit of PBAF [32] show increased R loop levels in cell-based assays. When PBRM1 deficient cells were treated with either ATR or PARP inhibitors in this study, cGAS/STING pathway activation was observed [32], implicating this pathway in the cross-talk between genome stability and innate immune signalling. Whether R loop accumulation in ARID1A deficient cells also activates cGAS/STING signalling hasn't yet been tested, but in another study, ARID1A-deficient cells showed increased cGAS/STING activation following treatment with ATM or CHK2 inhibitors [33], which could be mechanistically related.

5. SWI/SNF deficiency, double-strand break repair, and neoantigen formation

All three SWI/SNF complexes have been implicated in the repair of DNA double strand breaks (DSBs) through both homologous recombination and non-homologous end joining [1, 34]. Therefore, when SWI/SNF subunits are absent, impaired DSB repair activity leading to inefficient repair or the use of more mutagenic repair pathways could increase the probability of generating neoantigens. Of note, the ARID1A subunit of BAF promotes NHEJ through and interaction with the Ku heterodimer [35], and it would be interesting to explore the contribution of this role relative to its MMR activity in maintaining genome stability.

In addition, SWI/SNF complexes are important for repressing transcription near DNA DSBs and when this is impaired, rearrangements between actively transcribed genes are more frequent [36]. Translocations between actively transcribed genes leading to the expression of aberrant fusion genes represent another potential mechanism for neoantigen formation (for review, see [37]). Neoantigens arising from translocations have been shown to lead to immune responses, even when the tumour cells don't otherwise carry a heavy mutational load. These findings suggest that the increased likelihood of translocations between actively transcribed genes in SWI/SNF deficient cells could lead to the formation of neoantigens that can be therapeutically exploited (Fig. 3A). Collectively, therefore, through inefficient repair and failure to repress transcription at DNA breaks, SWI/SNF deficient cells have a higher probability of neoantigen formation. Furthermore, the likelihood of neoantigen formation increases with time. Whether and to what extent this plays a role during the evolution of cancer remains to be seen.

6. PBAF deficiency, CIN, aneuploidy, and immune responses

We previously found that the PBRM1 subunit of PBAF helps promote sister chromatid cohesion at centromeres and in its absence, cells are more likely to missegregate chromosomes ([38]; Fig. 3). More recently, we found that PBRM1 directs the PBAF complex to centromeres where it acts to prevent centromere fragility (Lane et al, unpublished). Importantly, PBRM1 was identified as a genetic determinant for chromosome instability (CIN) signature 1, in which whole arm or whole chromosome copy number changes are apparent [39], consistent with a defect in centromere function. This highlights the important role of PBRM1 in preventing CIN in cancer.

In contrast, we found no evidence of increased CIN in an HCT116 cell line with SMARCA4 deletion [40]. It is worth noting that the HCT116 cell line is already MMR deficient [41], so any potential impact of SWI/SNF loss on MMR, and therefore on neoantigen formation as described above, is not relevant in this system. Whether the cell line background is important for the lack of apparent CIN when SWI/SNF is deficient is is not immediately clear and requires more investigation, particularly through the use of additional cell line models.

Importantly, however, we found that loss of SMARCA4 in this system leads to changes in pathways that are associated with tolerance to aneuploidy [40], such that the end result – increased levels of aneuploidy in the mutant cells – is the same (Fig. 3). Moreover, there is evidence of higher levels of aneuploidy in SMARCA4 deficient lung and kidney cancers [40]. Collectively, these studies suggest that loss of SWI/SNF function in at least some cancers will be associated with aneuploidy and in some cases, CIN.

The interplay between CIN and the immune system and their impact on cancer progression is complex (Fig. 3). Lagging and broken chromosomes can activate the cGAS/STING pathway, leading to interferon signalling [42], which will promote anti-tumour immunity. However, CIN has also been shown to promote metastasis, and recent work demonstrated that chronic cGAS/STING activation leads to re-wiring of downstream pathways leading to an immune suppressive environment [43].

Loss of SWI/SNF subunits can be early events in the evolution of cancer (for example, [44, 45]). When early, it seems reasonable to assume that PBRM1 deficient (and perhaps SMARCA4 deficient) cancers showing elevated CIN will at some point undergo such rewiring leading to immune evasion (Fig. 3C). This raises the question whether the effect of PBRM1 loss on cGAS/STING signalling through its roles in maintaining the G2/M checkpoint or suppressing R loop formation contributes to anti-cancer immunity or response to ICI therapy. It is possible that the more relevant impact of PBRM1 on immune signalling – at least at later time points during cancer progression – will be through neoantigen formation.

7. Conclusions

The interplay between genome stability maintenance defects and immune responses is an important factor that will have implications for disease progression as well as response to immunotherapy. SWI/SNF complexes contribute to multiple pathways that maintain genome stability. In their absence, defective DNA repair, R loop resolution, DNA damage checkpoints, and chromosome segregation can all contribute to both innate and adaptive immune responses. The relative contribution of each of these genome maintenance roles to immune responses has yet to be determined and will likely vary depending on the SWI/SNF subunit involved, the tissue type, and the genetic context. Of note, other chromatin remodelling complexes contribute to genome stability, and are therefore likely to also affect innate and adaptive immune responses when defective.

As highlighted above, SWI/SNF deficiency can also lead to altered immune responses through defective transcriptional regulation. Indeed, in addition to directly regulating the expression of genes involved in immune signalling, changes in expression of other transcripts such as transposable elements can be important to immune activation. Unpicking the relative contribution of each of these activities to immune signalling and their importance for response to immunotherapy will be a major challenge in the field. This challenge is made even more difficult by the combinatorial complexity of the SWI/SNF complexes and the fact that the cells evolve and rewire pathways during the evolution of cancer.

Nevertheless, understanding how SWI/SNF activities that maintain genome stability interface with immune responses will have clinical importance. Therapies that damage DNA or override checkpoints are commonly used and can be deployed in combination with immune checkpoint inhibitor therapy. Understanding how this might impact SWI/SNF deficient cancers will open up new therapeutic approaches for these patients.

Funding Source
Cancer Research UK (C7905/A25715) and (A28724), Medical Research Council (MR/W001276/1).

Acknowledgements
We thank all members of the Downs lab for helpful discussions. Work in the Downs laboratory is funded by Cancer Research UK and the Medical Research Council.

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Subunit	Alternative name(s)	BAF	PBAF	GBAF	Domains
SMARCA4	BAF190A, BRG1	✓	✓	✓	QLQ, HSA, Helicase ATP-binding, Helicase C-terminal, Bromodomain
SMARCC1	BAF155	✓	✓	✓	SWIRM, SANT
SMARCD1	BAF60A	✓	✓	✓	SWIB/MDM2
SMARCD2	BAF60B	✓	✓	✓	SWIB/MDM2
SMARCD3	BAF60C	✓	✓	✓	SWIB/MDM2
BCL7A		✓	✓	✓	
BCL7B		✓	✓	✓	
BCL7C		✓	✓	✓	
ACTL6A	BAF53A	✓	✓	✓	
ACTL6B	BAF53B	✓	✓	✓	
ACTB	β-actin	✓	✓	✓	
SMARCC2	BAF170	✓	✓		SWIRM, SANT
SMARCB1	BAF47	✓	✓		
SMARCE1	BAF57	✓	✓		HMG-box
ARID1A	BAF250A	✓			ARID
ARID1B	BAF250B	✓			ARID
DPF1	BAF45B	✓			Zinc Fingers (CH2H type, PHD type 1, PHD type 2)
DPF2	BAF45D	✓			Zinc Fingers (CH2H type, PHD type 1, PHD type 2)
DPF3	BAF45C	✓			Zinc Fingers (CH2H type, PHD type 1, PHD type 2)
SMARCA2	BAF190B. BRM	✓	✓	✓	QLQ, HSA, Helicase ATP-binding, Helicase C-terminal, Bromodomain
SS18	SSXT	✓		✓	
SS18L1	CREST	✓		✓	
ARID2	BAF200		✓		ARID
PHF10	BAF45A		✓		Zinc Fingers (PHD Type 1, PHD Type 2)
PBRM1	BAF180		✓		Bromodomains. BAH, HMG-box
BRD7	BRD7		✓		Bromodomain
BRD9	BRD9			✓	Bromodomain
BICRA	GLTSCR1			✓	
BICRAL	GLTSCR1L			✓	

Table 1: SWI/SNF chromatin remodelling complex subunits. SWI/SNF subunits and their commonly used alternative names are listed. Subunits identified in the BAF, PBAF, and GBAF (ncBAF) complexes are indicated, and specialised domains as specified on UniProt [46] for each subunit are indicated.

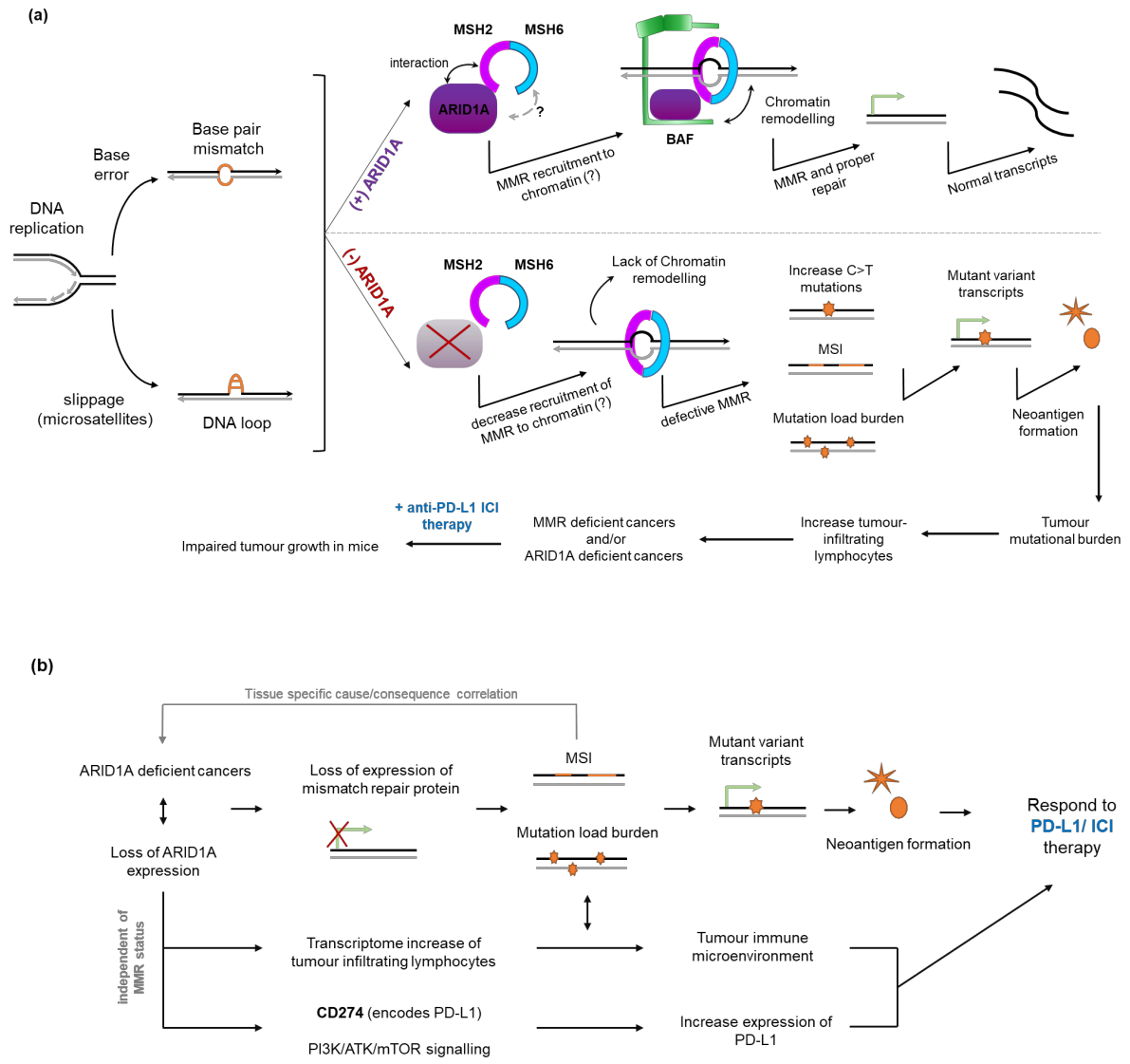

Figure 1. The multiple mechanisms linking ARID1A, mismatch repair and neoantigen formation with immunotherapy. (A) SWI/SNF promotes mismatch repair of DNA loops and/or mismatch base pair. The SWI/SNF subunit ARID1A interacts with MSH2. This could promote recruitment of the MSH2-containing complexes or facilitate remodelling in the vicinity of the lesion. In ARID1A-deficient cancers, MMR is impaired, either due to lack of chromatin activity or reduced MMR recruitment to chromatin, resulting in an increase of mutation load burden and microsatellite instability. These lead to production of mutant variant transcripts that act as potential neoantigens and affect the tumour microenvironment resulting in an increase of tumour-infiltrating lymphocytes, and consequently sensitising ARID1A-deficient cancers and/or MMR deficient cancers to immune checkpoint inhibitors. (B) ARID1A regulates gene expression leading to reduced DNA repair proteins and increased mutation load, thus generating mutant variant transcripts and forming neoantigens. ARID1A also regulates PD-L1 levels, which will influence the response of these cancers to immune checkpoint inhibitor therapy. These mechanisms are not mutually exclusive.

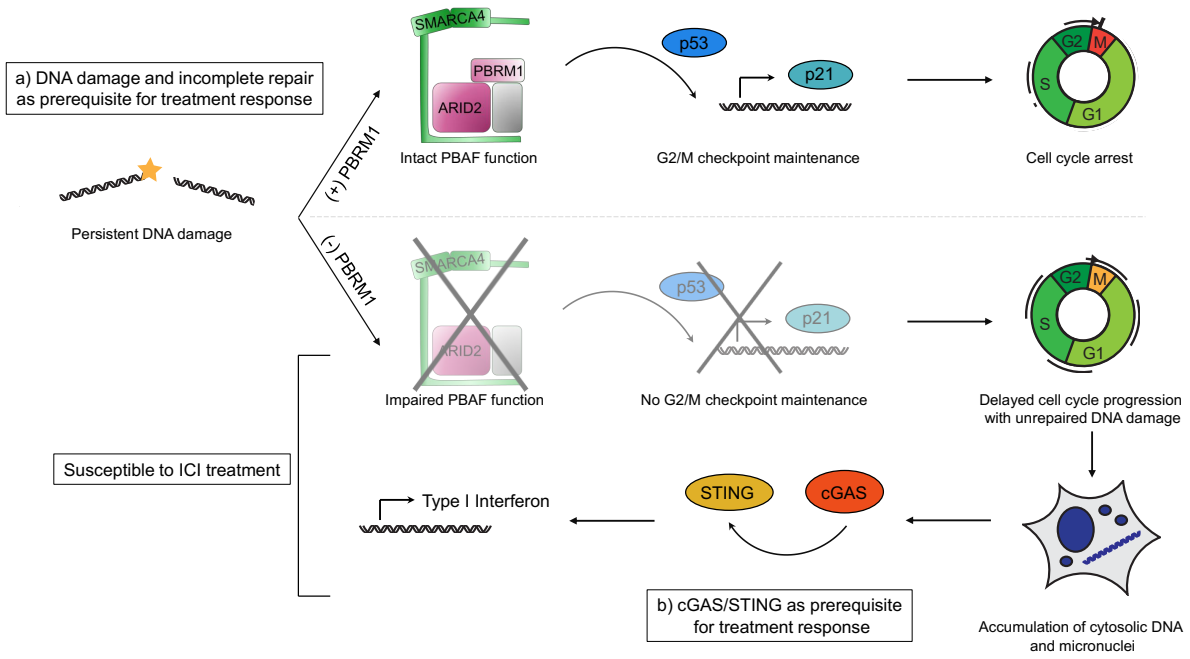

Figure 2. PBAF promotes G2/M checkpoint activation after DNA damage and its deficiency triggers an immune response. In the presence of PBRM1 and an intact PBAF complex, DNA damage leads to the p53-mediated activation of the G2/M checkpoint and cell cycle arrest. In contrast, if PBRM1 is deficient, the G2/M checkpoint is not maintained, allowing cells to, albeit delayed, progress through mitosis despite unrepaired DNA damage. As cells continue to cycle, this leads to an accumulation of cytosolic DNA species and micronuclei which then trigger the activation of the cGAS/STING pathway and the subsequent Interferon response. Both persistent DNA damage (Box a) and functional cGAS/STING signalling (Box b) are requirements for this consequence of PBRM1 loss to promote a favourable patient response to immune checkpoint inhibitor treatment.

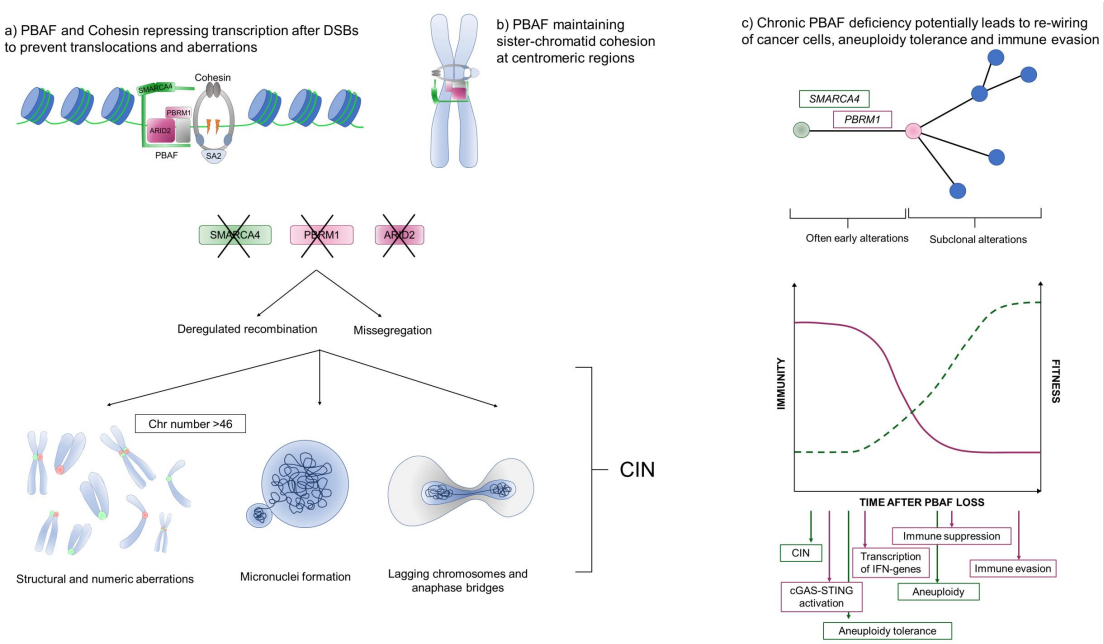

Figure 3. SWI/SNF in chromosomal instability and activation of immune signalling. (A) in SWI/SNF competent cells, PBAF and work co-ordinately to repress transcription around double strand breaks. This reduces the likelihood of translocations and other chromosomal aberrations arising from unfaithful DNA repair. (B) PBAF and cohesin also work together to ensure correct sister chromatid cohesion at centromeres and promote faithful chromosome segregation. Without PBAF subunits (SMARCA4, PBRM1 or ARID2), these processes (A and B) are not achieved efficiently, leading to deregulated recombination and mis-segregation. The resulting chromosomal instability takes the form of micronuclei formation, lagging and broken chromosomes and anaphase bridges following cell division leading to structural and numeric aberrations. These events can initiate cGAS-STING signalling, leading to interferon production. Neoantigen formation (as a result of structural aberrations) is also possible, which could act as a trigger of immune surveillance pathways and lymphocyte infiltration. (C) Notably, loss of SWI/SNF subunits is often, but not always, an early event in the development of cancer. This loss can lead to aneuploidy tolerance, allowing cells to explore different karyotypes without a fitness penalty. Over time, SWI/SNF deficient cells that are chronically aneuploid could undergo a re-wiring of signalling pathways initiated by cGAS-STING and subsequent immune evasion within a pro-metastatic environment, with poorer clearance of cancer cells. This suggests that response of SWI/SNF deficient cancers to immunotherapy could depend on the point during the cancer's progression that the patient is treated.