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SWI/SNF: Complex complexes in genome stability and cancer

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ABSTRACT

SWI/SNF complexes are among the most studied ATP-dependent chromatin remodeling complexes, mostly due to their critical role in coordinating chromatin architecture and gene expression. Mutations in genes encoding SWI/SNF subunits are frequently observed in a large variety of human cancers, suggesting that one or more of the multiple SWI/SNF functions protect against tumorigenesis. Chromatin remodeling is an integral component of the DNA damage response (DDR), which safeguards against DNA damage-induced genome instability and tumorigenesis by removing DNA damage through interconnected DNA repair and signaling pathways. SWI/SNF has been implicated in facilitating repair of double-strand breaks, by non-homologous end-joining as well as homologous recombination, and repair of helix-distorting DNA damage by nucleotide excision repair. Here, we review current knowledge on SWI/SNF activity in the DDR and discuss the potential of exploiting DDR-related vulnerabilities due to SWI/SNF dysfunction for precision cancer therapy.

1. Introduction

On a daily basis, each of our cells accumulates up to 10^4–10^5 DNA lesions that, if not adequately dealt with, can interfere with vital cellular processes such as transcription and replication, promoting genomic instability and eventually leading to tumorigenesis and premature aging [1,2]. DNA lesions are a fact of life as they originate, to a large extent, from the spontaneous chemical instability of DNA in the cell's aqueous milieu, such as hydrolysis of bases, or from chemical attack by intracellular metabolites, such as reactive oxygen species derived from oxidative respiration. Genomic stress is further aggravated by exposure to a range of environmental chemicals and radiation. Some of the best studied environmental genotoxic agents are ultra-violet (UV) light, ionizing radiation (IR) and inter-strand crosslinking agents, due to their relevance for cancer development. Paradoxically, the latter two are also commonly used to treat cancer in radiotherapy and chemotherapy, respectively. Because DNA cannot be replaced, removal of damage is vital to protect cells against genetic erosion and transcription and replication stress. Evolution equipped cells with a sophisticated portfolio of specialized DNA repair and DNA damage signaling pathways, collectively called the DNA damage response (DDR), to cope with the different types of DNA lesions [1,3]. A few of the different DNA repair pathways, relevant for this review, will be discussed in more detail below. The type of DNA lesion, its genomic location and chromatin environment, and the cell cycle phase determine which repair pathway is activated. Moreover, like all DNA-associated processes, DNA repair pathways have to overcome the physical barrier imposed by the condensed packaging of DNA into chromatin to efficiently access, detect, and repair lesions at any genomic location [4,5]. In recent years, the number of chromatin modifying and remodeling enzymes found important for efficient DNA repair has increased tremendously, evidencing that (re-)organization of the highly dynamic chromatin structure is an intricate and essential component of the DDR in vivo [6].

The nucleosome is the basic unit of chromatin, comprising approximately 146/147 bp of DNA wrapped around a histone octamer containing two copies of histones H2A, H2B, H3 and H4 [7]. Each nucleosome is stabilized by electrostatic interactions between the phosphate backbone of DNA and positively charged residues on histones, while short linker DNA segments link nucleosomes together. Folding and compaction of DNA into high-order structures is achieved by short and long-range interactions between nucleosomes, linker histone H1 and additional non-histone proteins. Dynamic rearrangement of the chromatin structure, via the concerted action of histone modifiers, histone chaperones, and ATP-dependent chromatin remodeling

Abbreviations: DDR, DNA damage response; DSB, double strand break; HR, homologous recombination; NHEJ, non-homologous end-joining; NER, nucleotide excision repair; UV, ultra-violet; IR, ionizing radiation; CPDs, cyclobutane-pyrimidine dimers; 6-4PPs, 6-4 pyrimidine-pyrimidone photoproducts; TC-NER, transcription-coupled NER; GG-NER, global genome NER; BAF, BRG1- or BRM-associated factors; PBAF, polybromo-associated factors; SWI/SNF, switching defective/sucrose non-fermenting

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complexes, regulates the access and activity of DNA-transacting enzymes, including that of DDR proteins [8]. In eukaryotes, many structurally related ATP-dependent chromatin remodeling proteins and complexes have been identified, including the four major families, SWI/SNF, INO80, CHD, and ISWI, many of which have been implicated in DDR [9–11]. Importantly, defects in both ATP-dependent chromatin remodelers [12] and DDR [2] are associated with tumorigenesis, but the interplay between these two with respect to cancer development is unfortunately only partially understood and currently an active field of research. In particular, the family of SWI/SNF chromatin remodeling complexes is frequently mutated in a wide variety of human cancers [13]. Therefore, we focus in this review on their emerging function in the DDR, specifically on their role in DNA double-strand break (DSB) repair and nucleotide excision repair (NER) and speculate on how this gained insight could be exploited for the development of new cancer prognostic markers and therapeutic interventions.

2. SWI/SNF ATP-dependent chromatin remodelers

2.1. SWI/SNF complex composition and chromatin remodeling function

SWI/SNF (switching defective/sucrose non-fermenting) complexes were named after the two phenotypes in yeast that led to their discovery, through genetic screening for genes that regulate mating type switching and activate sucrose fermentation pathways [14–16]. Evolutionary homologs of these multi-subunit protein complexes were later identified in *Drosophila* and mammals, and their role as major global regulators of transcription through ATP-dependent chromatin remodeling was firmly established [17–19].

SWI/SNF are heterogeneous complexes with the necessary skillset for diverse and specialized functions required in different cellular and developmental contexts [20,21]. Mammalian SWI/SNF complexes always contain one of two mutually exclusive, though structurally highly related ATPases: BRM/SMARCA2 or BRG1/SMARCA4 (Fig. 1a, Table 1). These proteins couple ATP hydrolysis with directional translocation over DNA, thereby either repositioning nucleosomes, exchanging nucleosomes histone dimers or evicting entire histone octamers [8,22] (Fig. 1b). In addition to the defining ATPase domain, BRM and BRG1 harbor domains for binding to actin and other proteins, such as the HSA and QLQ domains [23], and a bromodomain (BROMO) for binding to acetylated histones [24] (Table 1, Fig. 1c). Although BRG1 or BRM alone are sufficient for remodeling of nucleosomes in vitro [25], in the context of the cell the additional SWI/SNF core and accessory subunits play essential roles in targeting and regulating their remodeling activity [26,27]. Depending on their subunit composition, SWI/SNF complexes are divided into two main categories, BAF (BRG1- or BRM-associated factors) and PBAF (polybromo-associated factors) (Fig. 1a). In humans, SNF5/SMARCB1, BAF155/SMARCC1, and BAF170/SMARCC2 are core SWI/SNF subunits found in every SWI/SNF complex (Fig. 1a, dark blue ovals) [25]. BAF250A/ARID1A or BAF250B/ARID1B, BRD9 and SS18 are found exclusively in BAF complexes (Fig. 1a, grey ovals), while BAF200/ARID2, BAF180/PBRM1, PH10 and BRD7 are found solely in PBAF complexes (Fig. 1a, white ovals) [13,28]. Also, some accessory (family of) proteins are shared by BAF and PBAF, e.g., BAF57, β-actin, ACTL6 (A/B), BLC7(A/B/C) and DPF(1/2/3) (Fig. 1a, light blue ovals). Most subunits harbor one or more unique domain (Table 1), with which they tightly coordinate SWI/SNF function. For instance, subunits such as BAF180 and BRD7 harbor BROMO domains that allow SWI/SNF to interact with acetylated histones, while ARID and Zinc finger domains in ARID1A/B and ARID2 provide SWI/SNF with the ability to interact with specific DNA sequences [28–30].

In BAF complexes either BRM or BRG1 can be the catalytic subunit, whereas in PBAF that function is exclusively performed by BRG1. Many accessory subunits are encoded by sets of paralogs that are mutually exclusive and thus not present within the same complex: ACTL6A/B,

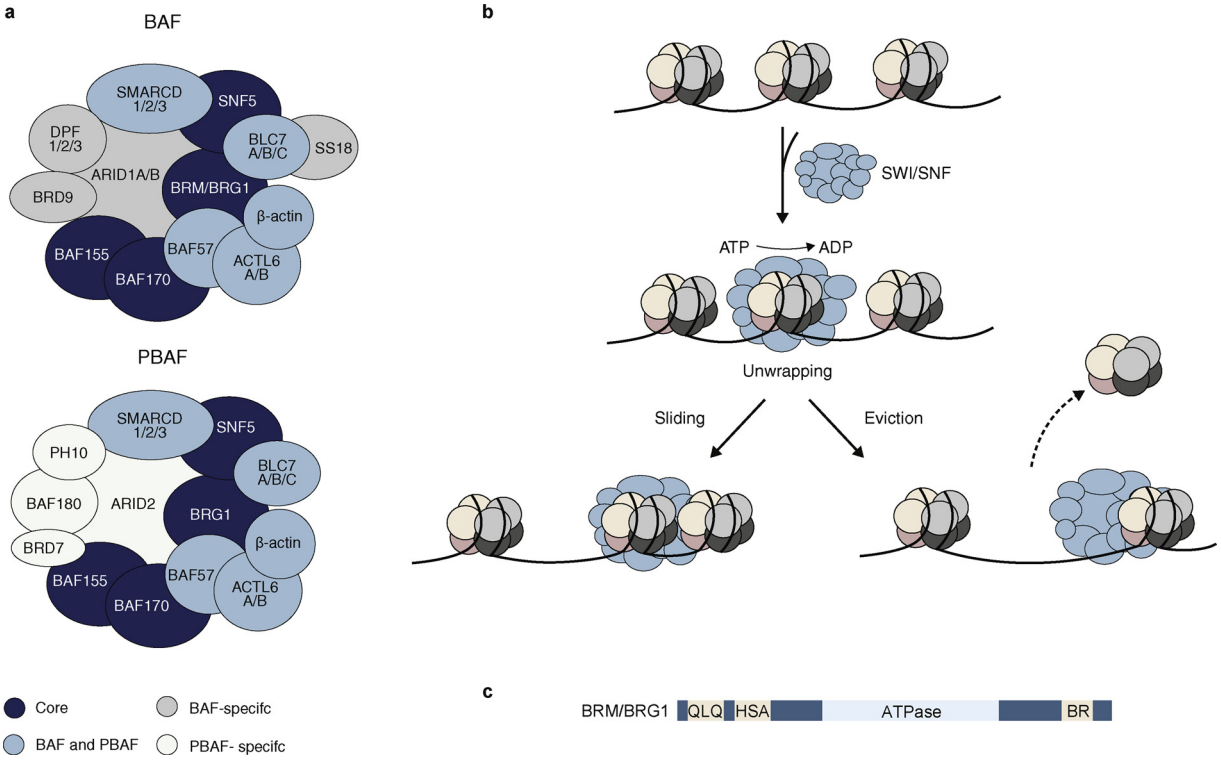

Fig. 1. SWI/SNF ATP-dependent chromatin remodeling complexes. (a) BAF and PBAF complexes are the two major subtypes of SWI/SNF complexes and are determined by their subunit composition [12,13,28,29,106,107]. (**b**) ATP-dependent chromatin remodeling activity of SWI/SNF complexes couples ATP-hydrolysis with directional movement of SWI/SNF that disrupts histone-DNA interactions at local nucleosomes [8,22]. (**c**) BRM and BRG1 share the same functional domains that regulate sequence-specific DNA (BR, Bromo, and HAS, Helicase/SANT-associated) and protein (QLQ, Gln-Leu-Gln motif) interactions.

Table 1
SWI/SNF subunits, domains and frequency of alteration in cancer.

Subunit	HUGO name	Synonyms	Domains	% Alteration in cancer
BRG1	SMARCA4	–	Bromo, ATPase, HAS, QLQ	Ovarian cancer (> 10%), medulloblastoma (5-10%), melanoma (5-10%), small cell cancer of the ovary (100%)
BRM	SMARCA2	–	Bromo, ATPase	Rhabdoid tumor (60%); lung (4.8-10%), breast (15%), gastric (15%) and bladder (15%) cancers
SNF5	SMARCB1	INI1, BAF47	COIL	Rhabdoid tumor (> 98%), epithelioid sarcomas (> 55%), familial schwannomatosis (30-45%)
BAF155	SMARCC1	–	CHROMO, SANT, COIL	Prostate cancer (30-31%)
BAF170	SMARCC2	–	CHROMO, SANT, COIL	Rarely mutated
ARID1A	ARID1A	BAF250A	ARID	Clear cell ovarian (50%), endometrioid ovarian (21-48%), breast (2.5%), liver (15%), bladder (17%), gastric (14-18%), lung (9.8%) cancer
ARID1B	ARID1B	BAF250B	ARID	Childhood neuroblastoma (7%), clear cell ovarian (> 10%), gastric, colorectal and liver cancer (5-10%)
ARID2	ARID2	BAF200	ARID, Zinc finger	Melanoma (5-15%), lung and colorectal (5-10%) and liver (5-14%) cancer
BAF180	PBRM1	–	Bromo, HMG	Renal cancer (41%), epithelioid sarcoma (83%)
BRD7	BRD7	–	Bromo	Breast cancer
BRD9	BRD9	–	Bromo	Rarely mutated
PH10	PH10	BAF45A	PHD finger	Rarely mutated
DPF1/2/3	DPF1/2/3	BAF45B/C/D	PHD finger	Rarely mutated
BAF57	SMARCE1	–	HMG, COIL	Familial spinal meningiomas (45%)
SMARCD1/2/3	SMARCD1/2/3	BAF60 A/B/C	SWIB	Rarely mutated
BCL7A/B/C	BCL7A/B/C	–	–	Non-Hodgkin's lymphoma (19.7%)
ACTL6A/B	ACTL6A/B	BAF53 A/B	Actin	Rarely mutated
SS18	SS18	SSXT	–	Synovial sarcoma (100%)

SWI/SNF subunits contain different protein domains to coordinate protein-protein or protein-DNA interactions [22]. Bromodomain (Bromo), important for the binding of acetylated histones. Coiled coil region (COIL) is a homodimerization domain. Chromatin organization modifier (CHROMO) domain is important for chromatin targeting. The Helicas/SANT-associated (HAS), SANT, ARID and HMG domains regulate sequence-specific DNA interactions, while the Gln-Leu-Gln (QLQ) motif, Zinc finger and PHD domains are involved in protein-protein interactions. SWI/SNF subunits alterations in cancer summarized here are extensively described in recent reviews [13,28,39,105].

DPF1/2/3, SMARCD1/2/3, and ARID1A/B [13,28]. Thus, the combination of different SWI/SNF subunits, encoded by at least 29 genes from 15 gene families [29], can potentially give rise to an undetermined number of distinct complexes of different biological functions, with specific combinations being unique to certain cell types. Cellular transitions, for instance during differentiation, can lead to dynamic reconfiguration of SWI/SNF complex composition. One example of this is the replacement of ACTL6A by ACTL6B, which is essential for proper neuron function during neuronal differentiation [30]. However, the impact of changes in subunit composition to the various functions of SWI/SNF complexes, in particular also to their function in the DDR, is far from understood.

2.2. Tumor suppressor functions of SWI/SNF

Mutations in genes encoding for SWI/SNF subunits are found in approximately 20% of all human cancers of various types [13,31] (Table 1). This suggests that SWI/SNF may act as a tumor suppressor, thus protecting against cancer development, likely by regulating processes that safeguard cellular homeostasis. It is therefore relevant to understand how SWI/SNF activity contributes to the tumorigenesis process. The first uncovered and most studied function of SWI/SNF is its intricate regulation of transcription. Mammalian SWI/SNF complexes regulate transcription by binding in close vicinity to promoters but also near other regulatory regions, such as enhancers [26,32]. By promoting or repressing the expression of specific genes, SWI/SNF complexes control vital cellular processes [32], including pluripotency of embryonic stem cells, cell cycle regulation and neuronal and hematopoietic cell differentiation [33]. Not only the ATPases BRG1 or BRM are needed for transcription regulation, but other SWI/SNF subunits play an important role in transcription by directly stimulating or inhibiting other transcriptional regulators. For instance, ARID1A/B and SNF5 can interact with the proto-oncogenic MYC protein to regulate the expression of its target genes, but can also modulate the expression of *MYC* itself [34,35]. Because *MYC* is an oncogene frequently overexpressed in cancer, tight control of its activity is desired, which could be potentially compromised in SWI/SNF-deficient cancers. Similarly, direct binding of BRM or BRG1 to the tumor suppressor RB1 [36] facilitates the repression of RB1 targets, such as E2F transcription factors, and promotes G1 arrest [37]. Thus, inactivation of SWI/SNF leading to loss of RB1 activity may result in uncontrolled cell cycle progression and favor the appearance of malignant phenotypes.

SWI/SNF has additional functions beyond the regulation of gene expression, which are vital to safeguard genome function and stability and to prevent cancer, as described extensively in recent reviews [28,31,38–40]. Examples include the regulation of alternative splicing, by favoring recruitment of the splicing machinery [41], and the regulation of decatenation activity of topoisomerase IIα (TOPIIα) [42]. Furthermore, the PBAF complex assists in sister chromatid cohesion by localizing at kinetochores of mitotic chromosomes [43] and by regulating centromeric cohesion in a transcription-independent manner [44]. Because centromeric cohesion is crucial for chromosome orientation and proper segregation, loss of not only BAF180 but also BRG1 results in cells with abnormal anaphase events, aneuploidy, and micronuclei [44,45]. All of these aberrant events are typical features of many cancers, suggesting that SWI/SNF-mediated centromere cohesion is required for tumor suppression.

3. SWI/SNF and the DNA damage response

SWI/SNF has been implicated in multiple DNA repair pathways, which may have significant repercussions for tumorigenesis of SWI/SNF-deficient cancers since DDR deficiencies often lead to genomic instability. Knowing which SWI/SNF factors are actively involved in protecting cells against DNA damage would allow us to have a more comprehensive understanding of which DDR-related cancer vulnerabilities could be targeted as a consequence of SWI/SNF deregulation. Moreover, it would help to predict chemotherapy sensitivity of SWI/SNF-deficient cancer cells in precision medicine procedures.

3.1. Double-strand break repair

SWI/SNF deficiency has been found to render yeast, *C. elegans* and human cells hypersensitive to DNA-damaging agents, including chemotherapeutic drugs such as doxorubicin and cisplatin, UV light and IR [46–51]. IR and chemotherapeutic drugs, the latter by interfering with

replication, cause DSBs. When not properly repaired, these DSBs can result in mutations and chromosomal aberrations (e.g., translocations) that underlie oncogenic transformation. DSBs are predominantly repaired by non-homologous end-joining (NHEJ) and homologous recombination (HR) [52]. NHEJ takes place during any stage of the cell cycle and is initiated when broken DNA ends are bound by the KU70/KU80 heterodimer, which recruits and orchestrates the activity of subsequent repair factors that process and join DNA ends by ligation. Alternatively, in late S or G2 cell cycle phase, DSB ends are bound by the MRE11-RAD50-NBS1 (MRN) complex, which, together with CtIP and EXO1, resects one strand to create 3′single stranded DNA overhangs to direct repair towards HR. In contrast to NHEJ, HR is more accurate and principally error-free, as it makes use of the sister chromatid as a template for homology-directed repair. MRN also recruits the phosphatidylinositol 3-kinase ATM, which phosphorylates histone H2AX (γH2AX) and many other proteins involved in repair and checkpoint signaling. RPA binds the resected single-stranded DNA and is subsequently replaced by the recombinase RAD51. The RAD51-nucleoprotein filament facilitates strand invasion to the homologous double-stranded DNA template of the sister chromatid, allowing DNA synthesis from the sister template and subsequent resolution of the recombined DNA strands. Yeast and mammalian SWI/SNF complexes have been implicated in both NHEJ and HR, as is also discussed in several previous reviews [9,10,38,53].

Depletion or inactivation of SWI/SNF subunits, including the ATPases BRG1 and BRM and core and accessory subunits, such as BAF155, BAF170, ARID1A/B and ARID2, sensitizes cells to DSB-inducing agents and reduces HR and/or NHEJ efficiency in fluorescent reporter assays [49,50,54–56]. Both BRM and BRG1 also rapidly localize to DSB sites, either induced enzymatically or by laser irradiation, in a manner that appears to be dependent on ATM-mediated signaling and post-translational modification of histones. ATM promotes the damage localization of SWI/SNF by phosphorylating histone H2AX [50] and by directly phosphorylating BRG1 and BAF170 [57]. In turn, BAF170 phosphorylation increases the interaction of SWI/SNF subunits with the early DDR protein BRIT1/MCPH1 [58], a protein that too helps recruiting SWI/SNF. Furthermore, recruitment of BRG1 to damaged sites was found to depend on an interaction with the tumor suppressor RB1 and the E2F1 transcription factor, which also localize to DSBs in an ATM phosphorylation-dependent manner [56]. Besides phosphorylation of histone H2AX, also H2B phosphorylation and H3 and H4 acetylation have been implicated in promoting the damage localization of SWI/SNF. For instance, BRG1 binds to damage induced γH2AX-containing nucleosomes by interacting with acetylated H3 histones through its bromodomain [59]. In addition, BRM recruitment to DSBs was reported to be stimulated by the activity of AMP-activated protein kinase, which phosphorylates H2B [60], and by the activity of acetyltransferases CBP/CREBBP and p300/EP300, which acetylate histones H3 and H4 at DSBs [54]. Next to the catalytic subunits, also other components of SWI/SNF are implicated in targeting SWI/SNF to damaged sites. For example, BRM recruitment to damage was found to depend on the SNF5, SMARCD3 and ARID1A/B subunits [49]. Thus, it is reasonable to assume that multiple mechanisms orchestrate, likely in a cooperative manner, the efficient recruitment to and function of SWI/SNF complexes at sites of DNA damage. Besides BRG1 and BRM, other mutually exclusive SWI/SNF subunits were shown to localize to DSB sites. For instance, ARID1A recruitment to DSBs depends on ATM signaling and direct interaction with ATR [55]. On the other hand, BAF180 is recruited independently of ATM.

The exact roles of SWI/SNF complexes in DSB repair remain convoluted, in part because of the multiple and sometimes even ambiguous activities that have been reported. For example, SWI/SNF may promote efficient damage signaling, as depletion of BRG1 and BRM was shown to reduce γH2AX levels early after IR [50]. However, other studies have reported increased [61] or persistent [62] γH2AX levels after BRG1 loss, indicative of a genuine repair defect. Indeed, SWI/SNF proteins are implicated in both NHEJ and HR, in yeast as well as mammals [31,38], which further confounds the dissection of their precise function in DSB repair. For instance, BRM and ARID1A/B were shown to stimulate recruitment of NHEJ factors, such as KU70/KU80 [49,54,60], while BRG1 and ARID1A appear to promote HR-associated DNA end resection and RPA and RAD51 loading [55,56]. However, another study suggested that BRG1, rather than affecting resection, by interacting with RAD52, stimulates HR by promoting the exchange of RPA for RAD51 [63]. Moreover, the PBAF subunit ARID2 was reported to interact with RAD51 and thereby to stimulate its loading onto DNA, independently of BRG1, but still in complex with BAF180 and other SWI/SNF proteins [62]. These studies suggest that SWI/SNF subunits may have functions in DSB repair beyond its motor function.

Despite a large amount of evidence suggesting that SWI/SNF stimulates DSB repair, it is unclear if this necessarily involves chromatin remodeling to provide access for repair factors to DNA. Some observations suggest that SWI/SNF activity promotes chromatin relaxation after DNA damage, such as increased H3 occupancy observed at DSB sites after ARID1A depletion [55] and reduced MNAse sensitivity of genomic DNA seen after BRM or BRG1 depletion [58]. However, it was also reported that deficient RAD51 loading due to BRG1 deficiency could be rescued by ATPase-mutant BRG1 [63], suggesting that this BRG1 function is independent of chromatin remodeling. Interestingly, instead of facilitating chromatin access, the PBAF complex was found to mediate transcription silencing near DSBs, involving polycomb complexes PRC1 and PRC2, and ATM-dependent mono-ubiquitylation of H2A, which promotes rapid NHEJ of a subset of DSBs [61]. Strikingly, this process required the catalytic activity of BRG1. Thus, considering that BRM and ARID1A/B are not part of PBAF, the different SWI/SNF complexes may have multiple functions in DSB repair, including promoting NHEJ by stimulating KU70/KU80 recruitment (via BAF) and chromatin remodeling-mediated transcription silencing (via PBAF). Moreover, SWI/SNF may promote HR by facilitating DNA end resection and/or RAD51 loading (via both BAF and PBAF) (Fig. 2). It thus seems possible that a BAFfling collection of different SWI/SNF complexes, some of which may even have opposing functions, are localized to or near DNA damage and simultaneously stimulate HR as well as NHEJ in the same cell. It could be that SWI/SNF complexes act in parallel at distinct sites dependent on the chromatin status or in concert at different distances with respect to the lesion. Obviously, more and innovative research is necessary to better understand how the proposed different mechanisms of recruitment and multiple activities at sites of damage are coordinated and which exact activities distinguish each separate SWI/SNF complex at sites of DSBs.

3.2. Nucleotide excision repair

Depletion or inactivation of SWI/SNF subunits significantly increases cellular sensitivity to UV and platinum drugs such as cisplatin [48,51,64], suggesting the involvement of SWI/SNF in NER. This versatile repair process detects and removes a wide range of unrelated helix-distorting lesions, such as bulky-adducts and drug-induced (e.g., cisplatin) crosslinks, as well as the main UV-induced photoproducts, cyclobutane-pyrimidine dimers (CPDs) and 6-4 pyrimidine-pyrimidone photoproducts (6-4PPs) [65,66]. This unique ability of the NER pathway not only protects cells against cancer and aging by preventing mutagenesis and genomic instability, but it also provides cancer cells with a defense line against chemotherapeutic platinum drugs [67,68].

Two distinct DNA damage recognition routes can trigger NER, depending on the location of DNA lesions. When RNA Polymerase II gets stalled by lesions in the transcribing strand of active genes, transcription-coupled NER (TC-NER) is initiated by the recruitment of CSB/ERCC6, CSA/ERCC8 and UVSSA proteins [66]. Lesions located anywhere in the genome are detected by global genome NER (GG-NER), which is initiated by the damage sensor complex XPC-RAD23B-CETN2 [65,66,69]. Although XPC can recognize a wide range of helix-

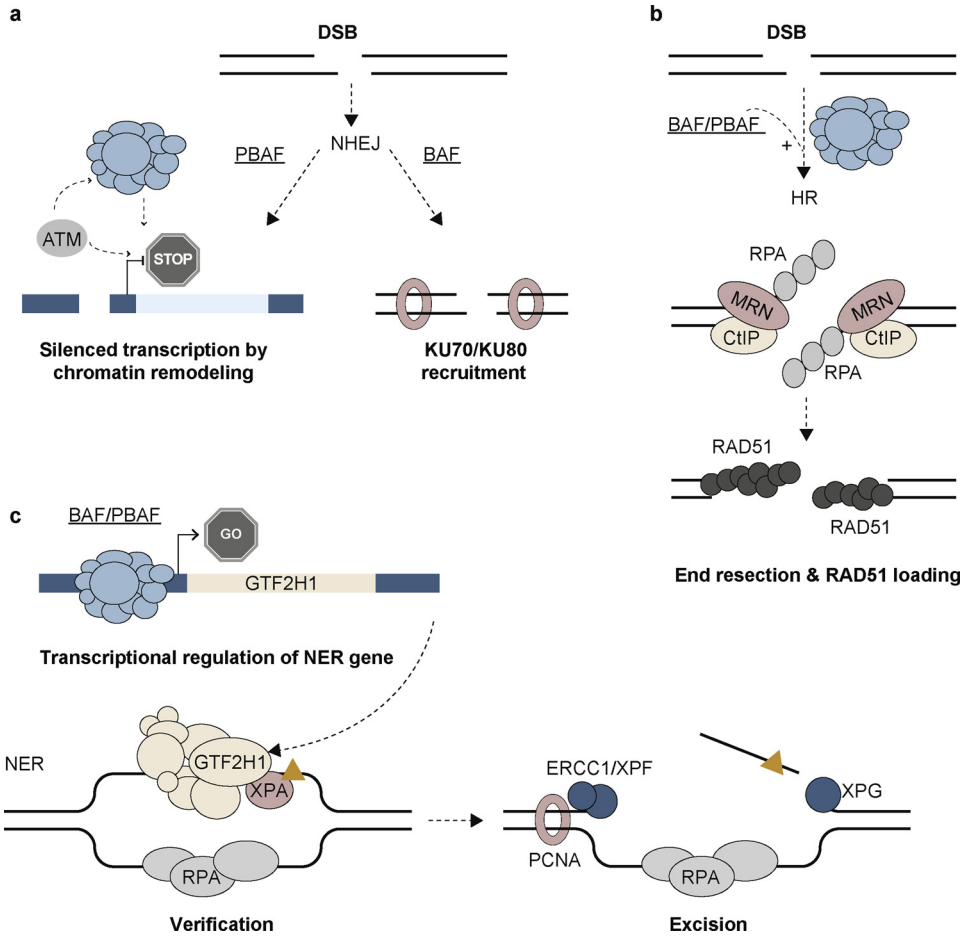

Fig. 2. SWI/SNF ATP-dependent chromatin remodeling complexes functions in DDR. (a) PBAF complexes, via their chromatin remodeling activity, were found to mediate transcription silencing near DSBs, in an ATM-dependent way. On the other hand, BAF complexes seem to have a distinct function in promoting NHEJ, by stimulating the recruitment of KU70/KU80. (**b**) Both BAF and PBAF complexes are implicated in promoting HR-associated end resection and/or RPA and RAD51 loading. (**c**) Unlike for NHEJ and HR, SWI/SNF activity only indirectly affects NER. BRM- and BRG1-containing SWI/SNF complexes promote the expression of the NER gene GTF2H1, which is essential for damage verification by TFIIH. In turn, verification is required for the assembly of late NER proteins on UV damage (XPA, RPA, ERCC1, XPF, XPG and PCNA).

distorting lesions, it requires the auxiliary function of the UV-DDB complex, consisting of DDB1 and DDB2, to specifically and efficiently recognize UV-induced photolesions, in particular CPDs. Following lesion detection, the ten subunit Transcription Factor IIH (TFIIH) complex is recruited to damage by interacting with XPC or UVSSA [70] and anchored through its XPB/ERCC3 and p62/GTF2H1 subunits. Using its XPD/ERCC2 helicase subunit, TFIIH then verifies the presence of genuine NER substrates [66,69], assisted by XPA. XPA and RPA stabilize this intermediate and adequately orient the structure-specific endonucleases XPF/ERCC4-ERCC1 and XPG/ERCC5. After dual incision, a stretch of 22–30 nucleotides is excised and the resulting single-stranded gap is filled by DNA synthesis and finally ligated [65,66,69].

Rearrangement of the nucleosome structure following UV damage [71] has triggered intense research on a possible function of ATP-dependent chromatin remodelers in NER by facilitating access to DNA. Numerous studies based on in vitro excision repair assays have shown that nucleosomes form a barrier to an efficient NER reaction and that DNA lesions are more easily repaired on naked than on chromatinized DNA [72–74]. Furthermore, the yeast SWI/SNF complex was found to increase accessibility and incision of damaged DNA within in vitro reconstituted mononucleosomes [75,76], suggesting that SWI/SNF could stimulate repair via chromatin remodeling activity. This idea is further supported by several studies in yeast and mammalian cells. For instance, yeast SWI/SNF subunits Snf5 and Snf6 were found to interact in a UV-dependent manner with Rad4, the yeast orthologue of XPC, and to stimulate UV-induced chromatin relaxation [77]. Studies using mammalian cells have also provided evidence that SWI/SNF and NER proteins interact, suggestive of a conserved function. Unfortunately, these studies have not been unambiguous in providing a precise mechanism of how mammalian SWI/SNF might be involved in NER. One study reported that BRG1 interacts with DDB2 in chromatin to facilitate XPC recruitment, suggesting that SWI/SNF might stimulate lesion detection, possibly by facilitating chromatin access [78]. However, this model is challenged by several other studies showing that SWI/SNF promotes late NER steps rather than early lesion detection. For instance, BRG1 itself was reported to be recruited to UV damage, in an XPC-dependent way, to promote the recruitment of late NER factors XPG and PCNA but not of XPC [79]. Accordingly, knockdown of BRG1 and BRM was described to impair recruitment of the late NER factor ERCC1 to cisplatin lesions without affecting XPC [51]. Moreover, SNF5 was found to interact with XPC, but not to regulate its recruitment but rather that of ATM [80]. Finally, depletion of ARID1A/B was found to reduce XPA recruitment, but not XPC recruitment, to damaged DNA [64]. Thus, there is substantial evidence supporting an evolutionarily conserved role of SWI/SNF in NER, even though contradicting findings obscure a clear deduction on its exact involvement.

The already challenging dissection of SWI/SNF function in NER is even further convoluted since several studies have suggested that loss of SWI/SNF subunits (BRM, BRG1, SNF5) impairs the removal of CPDs, but not of 6-4PPs [78–81]. It is difficult to envision how SWI/SNF deficiency could only impair CPD removal when SWI/SNF promotes the recruitment of NER factors, such as XPC and XPG, which are crucial for the repair of both CPDs and 6-4PPs. However, it has been observed that a specific mutation in the NER gene XPD affects the repair of CPDs more than that of 6-4PPs [82]. In addition, DNA damage is not distributed randomly and the repair kinetics of 6-4PPs and CPDs are dramatically different [83,84]. Since 6-4PPs are predominantly formed in internucleosomal DNA, they may not require chromatin remodeling by SWI/SNF to be efficiently processed. On the other hand, in another study it was shown that 6-4PPs removal is impaired after ARID1A/B depletion

[64].

In an attempt to gain more insight into the main role of SWI/SNF in the response to UV-induced DNA damage, and because most studies have focused on BRG1 or SNF5, we recently investigated a putative role of BRM in NER [85]. This study was also triggered by our previous finding that in the model organism *C. elegans* multiple SWI/SNF subunits, including BRG1/BRM, SNF5, BAF180, BAF155, and ARID1A/B, are essential for optimal UV survival [48] (and unpublished results). We found that knockdown of BRM in human cells impaired both GG- and TC-NER activity, to the same extent as did BRG1 depletion. Importantly, while recruitment of DDB2, XPC, and CSB to local UV damage sites was unaffected by BRM depletion, recruitment of proteins downstream of these damage sensors, i.e., TFIIH, XPA, and XPF, was severely impaired. These results are in line with the previously reported reduced recruitment of XPA, XPG, ERCC1, and PCNA following BRG1 or BRM depletion [51,64,79,85]. These observations thus indicate that SWI/SNF activity mainly facilitates late NER steps, rather than damage detection. Consequently, after depletion of SWI/SNF, the overall damage excision is reduced.

Strikingly, we were unable to observe BRM or BRG1 recruitment to local sites of UV damage, even using a dedicated UV-C laser to induce a high local concentration of DNA damage to which regular NER proteins localize [86]. Moreover, we could also not confirm the proposed interactions of BRM and BRG1 with TFIIH [85], nor with DDB2 and XPC (unpublished results). However, following BRG1 or BRM knockdown we observed a significant reduction in mRNA and protein levels of the TFIIH subunit GTF2H1, resulting in impaired TFIIH complex assembly. These observations suggest that the affected NER function upon SWI/SNF depletion is merely an indirect consequence of impaired *GTF2H1* gene expression, rather than a direct role of SWI/SNF in NER. Indeed, we found that both BRG1 and BRM associate with the promoter of *GTF2H1*, irrespective of whether there is UV damage or not, corroborating the idea that SWI/SNF promotes the expression of *GTF2H1*. Since assembly and functionality of the TFIIH complex were shown to depend on the cellular concentration of its subunits [87–89], it is therefore likely that reduced GTF2H1 protein levels limit the availability of fully assembled functional TFIIH complexes to act in transcription initiation and NER. Damage verification by TFIIH is crucial to the assembly of late NER proteins on UV damage. Thus, reduced damage verification as a consequence of SWI/SNF inactivation explains the reduced recruitment of XPA, ERCC1, XPF, XPG and PCNA to DNA damage and consequent hypersensitivity of cells to UV [51,64,79,81,85].

It is surprising to note that the role of SWI/SNF chromatin remodelers in both DSB repair and NER is rather convoluted, making it difficult, if not impossible, to draw a uniform mode of their action in the DDR. However, given the fact that the function of SWI/SNF in transcription regulation is also fairly ambiguous, with even opposing gene-dependent and chromatin-context-dependent effects, this may not be entirely unforeseen. Transcription regulation depends on the intricate interplay between cis-acting transcription-regulatory elements in the template DNA, availability of general and gene-specific transcription factors, activation by cell-intrinsic and environmental cues, post-translational chromatin modifications and chromatin compaction. This multi-layered control over gene expression likely explains the ambiguity of SWI/SNF (and possibly of other chromatin modifiers alike) in this process and its diverse and likely dynamic composition. However, unlike transcription that is commonly scheduled and takes place at a defined genomic locus, DNA repair has to occur at any given moment and anywhere in the genome [90] due to the stochasticity of DNA damage. This likely adds another degree of complexity, making it even more challenging to elucidate the multiple functions of SWI/SNF in the DDR.

4. SWI/SNF, DDR and cancer

4.1. SWI/SNF and NER deficiency in cancer

Since SWI/SNF is often mutated in cancer, we aimed at understanding whether cells with chronic SWI/SNF deficiency also have NER defects. Strikingly, we noticed that GTF2H1 levels were not altered in several established SWI/SNF-deficient cancer cell lines regularly used in lab research [85]. To understand the cause of this unexpected observation, we generated CRISPR/Cas9-mediated BRM and BRG1 knockout human fibroblasts. Surprisingly, upon extended culturing, we found that most cells with a permanent knockout of either SWI/SNF ATPase have the ability to restore expression of GTF2H1. However, we noticed that in some sub-populations of cells GTF2H1 expression remains low. Accordingly, we noticed that sensitivity to DNA damaging agents of BRM-knockout cells was directly linked to the expression levels of GTF2H1, as only cells that retained lowered GTF2H1 expression were hypersensitive to UV and cisplatin. Thus, SWI/SNF inactivation creates a potential vulnerability of cells to DNA damaging agents, as a consequence of GTF2H1 downregulation (Fig. 2). Therefore, we propose that GTF2H1 expression levels could serve as a potential biomarker to screen SWI/SNF cancers for increased sensitivity to chemotherapeutics drugs, such as cisplatin, even before therapy begins. However, efforts are needed to test if indeed GTF2H1 levels are reduced across primary SWI/SNF cancers and to determine its suitability as a predictive marker for cisplatin sensitivity.

The ability of chronic BRM- and/or BRG1-deficient cells to adapt and upregulate GTF2H1 levels likely explains why established SWI/SNF-deficient cancer cell lines do not show reduced GTF2H1 levels. Also, it could explain why contradicting observations exist regarding cellular sensitivities to DNA damage of SWI/SNF-deficient cancer cells [91,92]. Similar adaptation to the loss of one or more SWI/SNF ATPases or subunits has been described for other regulatory functions of SWI/SNF outside DNA repair. It appears that BRG1 and BRM can at least partially compensate for each other's essential functions [93–96], as cells with inactivating mutations in BRG1 strongly rely on BRM to sustain a minimal degree of SWI/SNF functionality to support cellular viability [93,94]. Also, the viability of ARID1A mutant cancer cells strongly depends on the, otherwise non-essential, ARID1B subunit [97]. How cells compensate for the loss of BRM and/or BRG1, ARID1A and/or ARID1B, is yet unknown. BRM and BRG1 are similarly distributed across regulatory regions of the genome where they act either cooperatively or competitively to regulate transcription [98]. Interestingly, loss of either ATPase at certain regions often leads to concomitant loss of the other ATPase as well. Depending on which other transcriptional regulators are associated with these regions, which can be either activating or repressing, transcription of genes can be up- or down-regulated when SWI/SNF is inactivated. The existence of such multiple transcriptional control layers, including other families of ATP-dependent chromatin remodelers, could explain why cells are able to (partially) compensate for the loss of SWI/SNF activity. Possibly, in time, GTF2H1 is also upregulated in chronic SWI/SNF-deficient cells due to the activity of such yet unidentified secondary transcriptional activator (s). In any case, identification of the compensatory mechanisms and chromatin regulators that lead to GTF2H1 upregulation is fundamental. Hopefully, such insight would allow us to exploit these compensatory mechanisms therapeutically by rendering SWI/SNF-deficient cancer cells specifically hypersensitive to DNA damaging treatments.

Thus far, the relevance of only a selected group of SWI/SNF subunits to the DDR has been studied while many more subunits are found to be mutated or silenced in cancer (Table 1). The involvement of these subunits in DNA repair is not yet known, but dissecting their precise function in response to DNA damage could contribute to a more comprehensive understanding of SWI/SNF-deficiency in cancer. Therefore, future studies should consider whether additional subunits are relevant to DNA repair as well. In addition, it is also interesting to study whether

SWI/SNF is involved in additional DNA repair pathways as well and what its precise activity in each repair pathway is. For instance, besides DSB repair and NER, BRG1 has been found to support repair of interstrand crosslinks, together with BRCA1 and FANCD2, to help maintain the differentiation status of human mammary epithelial cells and suppress breast cancer [99]. Also, a stimulatory function in base excision repair in vitro and yeast cells was proposed [100]. However, its exact involvement in these repair pathways is even less clear and scrutinized than in DSB repair and NER.

4.2. Therapeutic perspectives

Given the high incidence of SWI/SNF mutations in different cancers and their involvement in multiple DDR pathways, it would be advantageous to aim future studies at therapeutically exploiting defects in DNA repair due to SWI/SNF-deficiency. For instance, the importance of SWI/SNF to HR suggests that SWI/SNF-deficient cancers could be specifically treated with PARP inhibitors (PARPi), which efficiently and specifically kill HR-deficient cancers cells and are currently also clinically applied against BRCA1-deficient cancers [101]. Indeed, it was shown that ARID1A-deficiency sensitizes cancer cells to PARPi both in cultured cells and in vivo [55]. A recently published functional HR assay on *ex vivo* fresh tissue samples, RECAP [102], has proven to reliably identify breast cancer tumors with HR-deficiency that are thus sensitive to PARPi treatment. Moreover, with this novel method, the use of PARPi could potentially be extended beyond cancers harboring germline mutations in *BRCA1/2*. Hence, it could be advantageous also to test the HR capacity of SWI/SNF-deficient tumors and to use this assay to predict their sensitivity to PARPi. To increase efficacy, such therapeutic strategies that exploit DDR defects may be combined with other recently discovered therapeutic approaches targeting other SWI/SNF-deficiency-induced susceptibilities. Interestingly, ARID1A-deficient cells are also vulnerable to other forms of treatment, such as small molecule inhibitors of HDAC6, whose upregulation in ARID1A-deficient ovarian cancers inactivates p53 and protects cancer cells from apoptosis [103]. Also, ATR inhibitors selectively kill ARID1A-deficient cancer cells due to defects in TOPIIα and cell cycle activity that activate ATR-dependent checkpoint signaling [104]. Since SWI/SNF-deficient tumors may be hypersensitive to DNA damage due to defects in DNA repair pathways [49,85], it would thus be beneficial to consider combined therapeutic approaches utilizing PARP, ATR or HDAC6 inhibitors and cisplatin in SWI/SNF cancers.

5. Conclusions

Due to its many functions, it is highly plausible that SWI/SNF complexes affect the DDR besides merely facilitating access of repair factors to DNA damage. However, it is currently a challenge to disentangle their precise activities in DDR from their many other cellular functions, including general maintenance of chromatin architecture. We cannot yet answer with certainty whether different SWI/SNF complexes are specific for different DDR pathways, why certain subunits are more frequently associated with specific tumor tissues than others and whether this is relevant to genome stability or not. Furthermore, loss of SWI/SNF activity can be compensated by, at least in part, other SWI/SNF complexes or redundant mechanisms that take over in the absence of SWI/SNF activity. SWI/SNF-deficient cancer cells likely rely on these “backup” mechanisms, which could allow them to acquire resistance to certain cancer therapies but will also make them specifically vulnerable to newly developed therapies. Mapping of the exact contributions of SWI/SNF in DDR and its functionally redundant backup mechanisms is therefore crucial to understand how SWI/SNF inactivation promotes tumorigenesis and to develop efficient and precise therapies for SWI/SNF cancers.

Conflict of interest

The authors declare that there are no conflicts of interest.

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