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Snf2-family proteins: chromatin remodellers for any occasion

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Chromatin facilitates the housing of eukaryotic DNA within the nucleus and restricts access to the underlying sequences. Thus, the regulation of chromatin structure provides an excellent platform for regulating processes that require information stored within genomic DNA. Snf2 proteins are a family of helicase-like proteins that direct energy derived from ATP hydrolysis into the mechanical remodelling of chromatin structure. Here, we highlight some of the recent discoveries regarding this family of proteins and show Snf2 proteins have roles in many aspects of genetic metabolism. Recent developments include new insights into the mechanism for nucleosome spacing and histone dimer exchange; together with growing evidence for the involvement of Snf2 proteins in DNA repair.

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Introduction

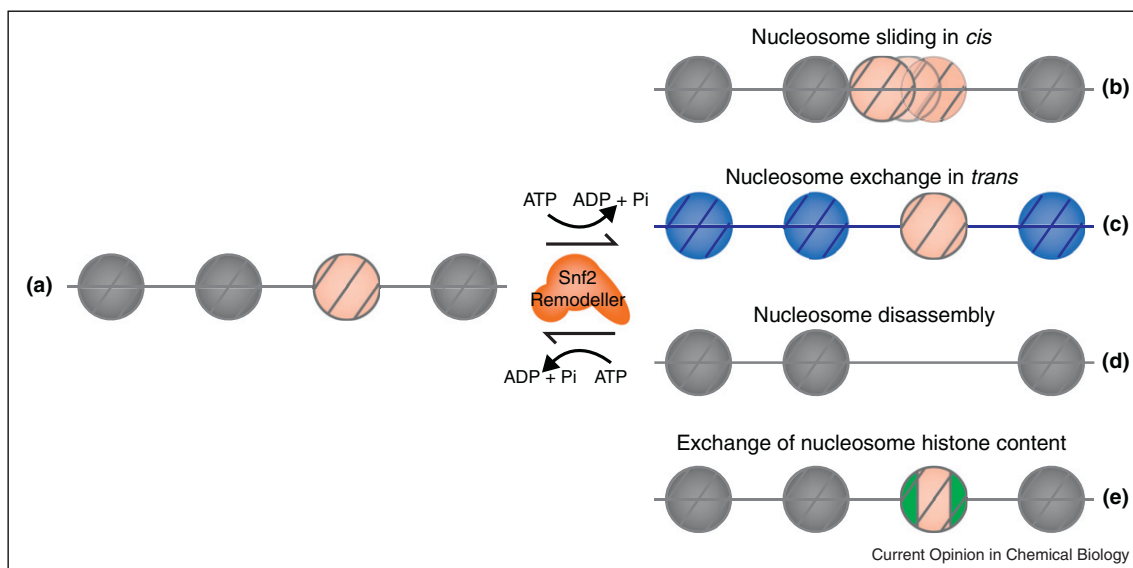
Eukaryotic DNA is packaged into a highly condensed nucleoprotein structure called ‘chromatin’. Chromatin is a hierarchy of structures that represent different levels of compaction, with the first level of compaction and fundamental repeating unit being the nucleosome. Canonical nucleosomes consist of an octamer of histone proteins – two copies each of core histones H2A, H2B, H3, and H4 – around which the DNA is wrapped almost two times in a superhelical manner (PDB ID: 1KX5) [1]. Nucleosomes and higher-order chromatin structures provide an efficient means of compacting eukaryotic genomes for storage within the confines of the nucleus. However, they also pose a significant barrier to processes that require access to the underlying DNA sequences, such as transcription, replication, recombination, and DNA repair. Factors that alter chromatin structure are integral to the regulation of all the major genetic processes. These

include the regulation of nucleosome assembly by histone chaperones, the covalent modification of histone proteins and DNA, targeted incorporation of variant histone proteins, and ATP-dependent mechanical remodelling of nucleosomes by Snf2-family proteins. These mechanisms are not exclusive to one another and interplay between them is common. There are many excellent reviews covering the topics of histone and DNA modifications [2–5], as well as the mechanisms and biology of histone chaperones [6,7]. Here, we focus on the Snf2 family of ATP-dependent chromatin-remodelling machines, highlighting recent work at the forefront of our understanding of their mechanisms and biological functions.

Snf2 helicase-related ATPases drive chromatin-remodelling machines

Snf2-family proteins are so-called owing to the presence of a domain that is homologous to the helicase-like ATPase domain of the *Saccharomyces cerevisiae* Snf2 protein [8]. This domain, the Snf2 domain, consists of two tandem RecA-like folds and contains seven conserved helicase-related sequence motifs that classify it as part of the Superfamily 2 (SF2) grouping of helicase-like proteins. Snf2 proteins form their own family within SF2 owing to additional conserved sequence motifs [9,10]. The Snf2 family can be further divided into subfamilies based on similarities within these Snf2-specific motifs [10]. Snf2 proteins are not *bona fide* helicases, lacking the ability to separate nucleic acid strands. Instead, Snf2 proteins are DNA translocases that apply an ATP-dependent torsional strain to DNA, which provides the necessary force to remodel nucleosomes or in some cases other DNA–protein complexes [11,12]. How this force is directed into the remodelling reaction is still not well understood and is likely to be specific for different remodellers. This is best demonstrated by the diverse range of outputs associated with different remodelling proteins; including, changes in the translational position of nucleosomes along DNA *in cis*, either towards or away from a given barrier, such as DNA ends or neighbouring nucleosomes; the transfer of histones between DNA molecules *in trans*; the assembly/disassembly of nucleosomes; and the exchange of the histone content within a nucleosome, such as the incorporation of specific histone variants (Figure 1). These outputs are probably directed by accessory domains and/or interacting proteins outside of the Snf2 domain. Indeed, numerous additional protein domains have been identified within the primary sequences of Snf2 proteins and many Snf2 proteins reside in large multi-protein complexes [13].

Figure 1



The different outputs of Snf2-protein chromatin-remodelling machines. The different remodelling reactions (a being converted to b–e) are often catalysed by specific subfamilies of Snf2 proteins. The reverse reactions (b–e being converted to a) are also possible and are often catalysed by a different Snf2 protein. This suggests that Snf2 domains in different Snf2-protein subfamilies have been tuned for different activities; either by variation in the sequence of the Snf2 domain itself or by additional protein domains and/or interaction partners. Nucleosomes are represented as coloured circles, the grey or blue lines represent DNA. Green segments in (e) indicate nucleosomes with altered histone content.

Roles for Snf2 proteins in regulating the distribution of histone variants

The majority of nucleosomes are composed of the four canonical histone proteins. However, within a subset of nucleosomes one or more of the core histones are replaced with a variant histone. The incorporation of histone variants into nucleosomes allows the marking of specific nucleosomes or domains of nucleosomes within the genome for a specific purpose [14]; such as transcription activation/repression or the delineation of specific chromatin structures, including centromeres and telomeres. Recently, the roles of several Snf2 proteins in maintaining chromatin domains that contain specific histone variants have been reported.

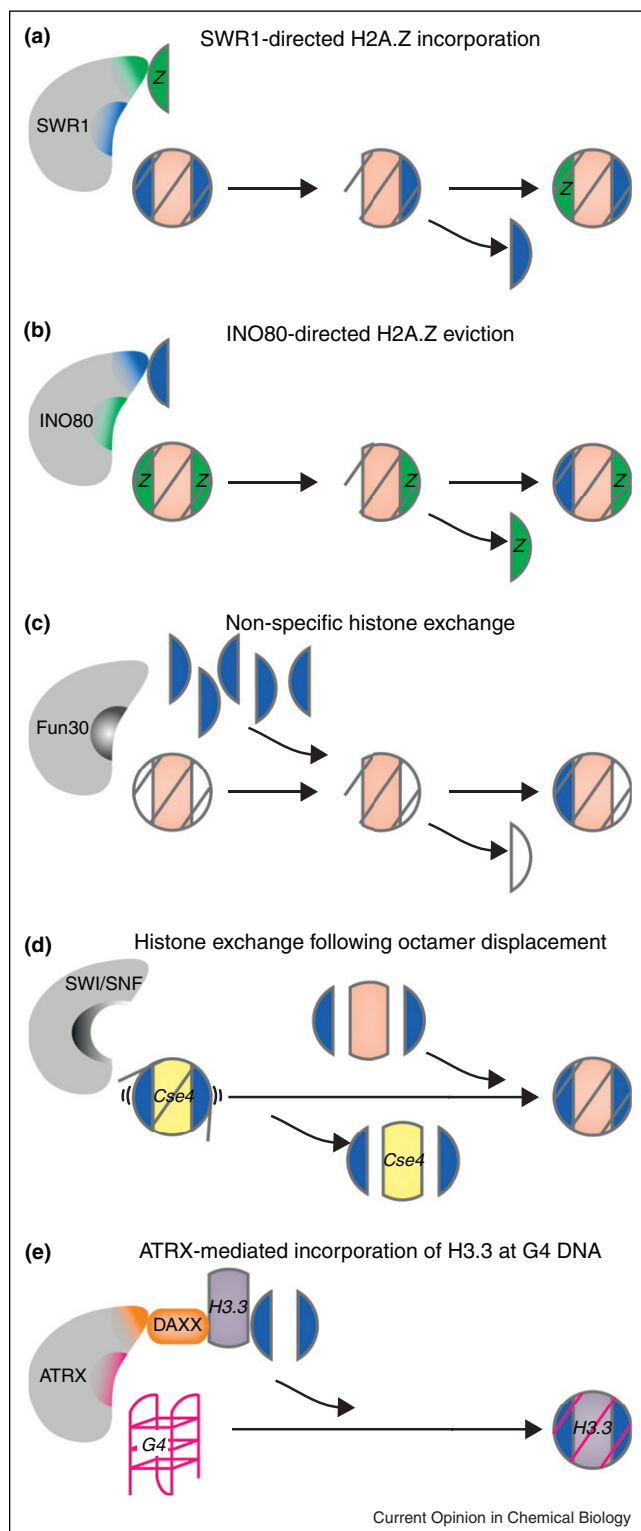
Swr1-like proteins regulate the incorporation and removal of H2A.Z

H2A.Z (Htz1 in yeast) is a highly conserved variant of canonical H2A. Typically, H2A.Z is enriched in the promoter-proximal regions of genes [15]; however, it has also been found in heterochromatic regions [16]. The transcription start site (TSS) of genes, particularly in yeast, is generally characterised by a nucleosome-depleted region flanked by two well-positioned H2A.Z-enriched nucleosomes, known as the +1 and –1 nucleosomes [15]. This distinct patterning suggests important roles for H2A.Z in regulating transcription and other nuclear processes.

The Snf2 protein Swr1 forms the core of a megadalton-sized complex that is conserved from yeast (SWR1) to humans (SRCAP), and its role in depositing H2A.Z into chromatin has been widely studied [17]. However, the mechanism of this incorporation has not been elucidated. Luk *et al.* [18^{••}] have demonstrated that SWR1 catalyses the replacement of H2A–H2B dimers with H2A.Z–H2B dimers in a stepwise unidirectional manner (Figure 2a), where heterotypic nucleosomes containing one H2A.Z–H2B and one H2A–H2B dimer are formed first before a second round of exchange produces homotypic nucleosomes containing two H2A.Z–H2B dimers. This work leads to a model in which SWR1 specifically recognises the canonical H2A in nucleosomes and is only activated by free H2A.Z–H2B dimers into a state competent for histone exchange. This explains how SWR1 is able to maintain specificity *in vivo* where a large excess of canonical H2A–H2B dimers are present.

The Swr1-like yeast Ino80 protein resides in the 15 subunit INO80 complex that has roles in transcription regulation, the DNA-damage response (DDR) and replication progression [17,19]. Ino80 is well conserved through eukaryotic evolution and in humans is also part of a large complex, with many subunits conserved with the yeast counterpart [19]. The Peterson group [20^{••}] report that deletion of Ino80 in yeast leads to aberrant spreading of H2A.Z within the genome, which negatively

Figure 2



Different mechanisms for exchanging the histone content within nucleosomes. **(a)** SWR1 specifically removes canonical H2A (blue) from nucleosomes and replaces it with H2A.Z (green). **(b)** INO80 removes H2A.Z and replaces it with H2A. **(c)** Some Snf2 proteins, such as yeast Fun30, exchange histones without apparent specificity. This may be

affects DNA repair mechanisms and replication fork stability. Furthermore, they show that INO80 can replace nucleosomal H2A.Z–H2B dimers with canonical H2A–H2B dimers *in vitro*, with a specificity converse to that of SWR1 (Figure 2b) [20**]. Leading to the hypothesis that INO80 plays a direct role in regulating the genomic distribution of H2A.Z, which is essential for genome stability.

Another member of the Swr1-like subfamily of Snf2 proteins is yeast Fun30 (Function Unknown 30). Like SWR1 and INO80, Fun30 has histone exchange activity, but appears less specific in its action [21]. Recent studies on Fun30 homologues in other species show it is involved in regulating the histone content of chromatin [22,23]. It is possible that Fun30 acts as a non-specific ‘histone exchanger’ in which its action is driven by histone availability (Figure 2c).

SWI/SNF is needed for centromeric stability

Analogous to the role of INO80 in removing H2A.Z, the yeast SWI/SNF complex has been shown to restrict the distribution of Cse4-containing nucleosomes to centromeric regions [24]. Cse4 is the budding yeast centromeric H3 variant (known as CENP-A in other species). A single Cse4-containing nucleosome marks the location of the centromere in yeast, whereas centromeric regions in higher eukaryotes contain multiple CENP-A nucleosomes. Loss of SWI/SNF results in spreading of Cse4 throughout the genome, causing defects in the cell-cycle and chromosome segregation. The SWI/SNF complex was also shown to preferentially disassemble Cse4-containing nucleosomes *in vitro* (Figure 2d). Together, this provides evidence for SWI/SNF having an active role in removing Cse4 from ectopic locations. However, specificity in this case may derive from the reduced stability of Cse4-containing nucleosomes and targeted recruitment of the SWI/SNF complex rather than specificity of the enzyme itself for this histone variant. The contrasting mechanisms for influencing the distribution of histone variants adopted by SWR1, INO80, Fun30, and SWI/SNF (Figure 2a–d) may help to explain why several remodelling enzymes are implicated in controlling CENP-A distribution [25].

ATRX facilitates H3.3 deposition at telomeres

The Snf2 protein ATRX is so named because the human ATRX gene is frequently mutated in X-linked alpha thalassaemia/mental retardation syndrome (ATR-X syndrome). Recent studies [26,27**,28*,29] have implicated

used to dilute histone variants (white) within chromatin when there is an available excess of another histone, represented as canonical H2A in blue. **(d)** Unstable nucleosomes, such as those containing Cse4 (yellow), may be completely removed by SWI/SNF, allowing an alternative nucleosome to be assembled in its place. **(e)** ATRX recognises G4 DNA (magenta) and may incorporate H3.3 nucleosomes (purple and blue) at these sites via an interaction with DAXX.

mammalian ATRX in the incorporation of the histone H3 variant H3.3 at telomeres. Mammalian histone H3.3 differs from core H3 (H3.1/H3.2) by just 4 or 5 amino acids. H3.3 is expressed and incorporated into chromatin throughout the cell cycle, whereas H3.1/H3.2 are expressed only during S-phase and are incorporated into chromatin in a replication-dependent manner [30,31]. H3.3 was previously thought to be deposited onto DNA by the histone chaperone HIRA to mark transcribed regions [30,31]. However, in mouse embryonic stem cells (MESECs), genome-wide analysis of H3.3 distribution by Goldberg *et al.* [27**] and immunofluorescence studies by Wong *et al.* [29,32] have shown that H3.3 is also enriched at telomeres in an ATRX-dependent manner. ATRX is associated with the histone chaperone DAXX, which specifically binds H3.3 [26,28*,33], and the ATRX-DAXX complex can specifically assemble H3.3 containing nucleosomes *in vitro* [28*]. One model for how ATRX targets H3.3 incorporation *in vivo* is based on the finding that ATRX binds G-rich repeat sequences, which are prevalent in telomeres [34]. These repeat sequences have a predisposition for forming G-quadruplex (G4) structures, and ATRX preferentially binds to G4 DNA *in vitro* [34]. Such abnormal DNA structures are destabilising for the genome and it is enticing to think that ATRX is responsible for stabilising G-rich regions into regular chromatin structures by remodelling G4 DNA and incorporating H3.3-containing nucleosomes (Figure 2e). Indeed, the loss of ATRX leads to telomere instability [29].

Molecular mechanisms of Snf2 proteins with nucleosome spacing activity

The nucleosome-spacing activity of the Chd1 (Chromodomain Helicase DNA-binding protein 1) and ISWI (Imitation Switch) subfamilies of Snf2 proteins is well established [35,36]. Generation of correctly spaced nucleosomes is likely to be crucial for genome stability, particularly after the action of polymerases and other molecular machines.

Human ACF (an ISWI-containing complex) acts as a dimeric motor that is highly regulated by nucleotide binding, and moves nucleosomes bidirectionally while continuously sampling either side of the nucleosome in order to generate a regular spacing between nucleosomes [37,38]. A comprehensive review of the mechanisms of ISWI remodellers is covered in [39]. Chd1 and ISWI enzymes share several common properties; they both require nucleosomes bearing flanking ('linker') DNA and the histone H4 tail for activity; and in yeast, combined deletion of their respective genes, but not the individual deletions, results in synthetic growth defects, indicating overlapping roles [36]. Thus, it will be of interest to determine if Chd1 proteins also act as dimeric motors; or have they evolved an alternative pathway for generating regularly spaced nucleosomes?

Although these questions remain unanswered, significant insight into the structural basis for regulation of Chd1 has been provided by two recent studies [40**,41]. Chd1 is comprised of a tandem N-terminal chromodomain, a Snf2 domain and a C-terminal DNA-binding domain (Chd1-DBD). The crystal structure (PDB ID: 3MWY) of the combined chromodomains and Snf2 domain from Chd1 [40**] is the largest fragment containing a Snf2 domain to have its structure determined to date. The structure reveals the chromodomains are in direct contact with the Snf2 domain and maintain it in a state incompetent for ATP-hydrolysis (Figure 3). Hauk *et al.* [40**] postulate that the chromodomains act to prevent inadvertent stimulation of the Snf2 domain by DNA, which is supported by biochemical analysis of several Chd1 mutants. The structure of Chd1-DBD (PDB ID: 2XB0) [41] has revealed previously unrecognised structural homology with the DNA-binding HAND-SANT-SLIDE (HSS) domain found in ISWI proteins [42], providing additional evidence of a shared mode of action between these enzymes. This is strengthened by the recent DNA-bound structure of the HSS domain of yeast Isw1 [43] that shows a mode of DNA binding similar to that predicted for Chd1-DBD by mutagenesis and *in silico* modelling [41].

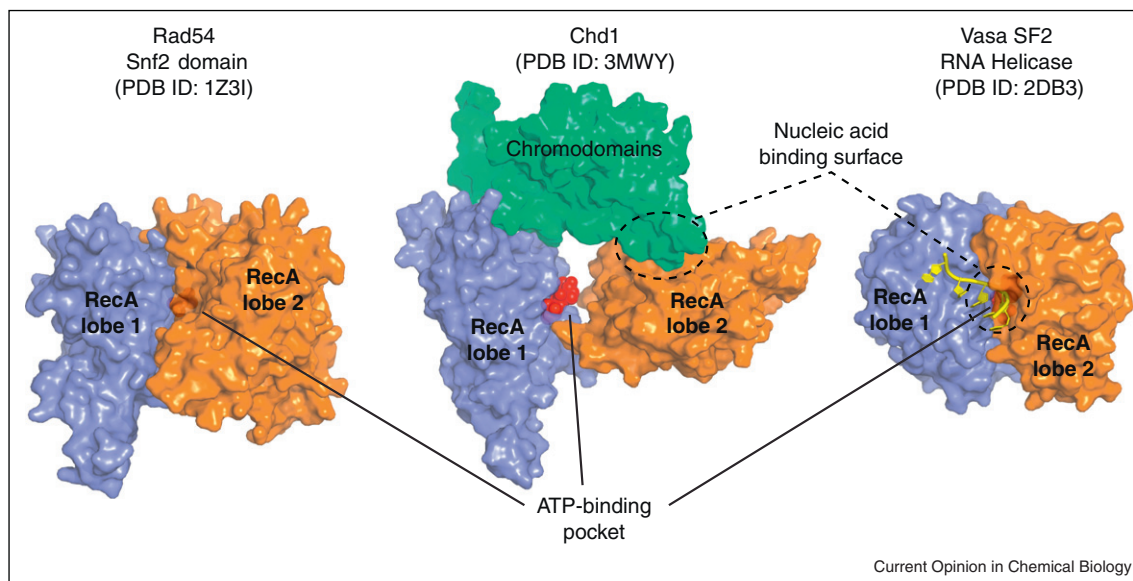
Very recently, the INO80 complex has also been shown to space nucleosomes [44*]. Like Chd1 and ISWI, INO80 is dependent on linker DNA for its activity, but lacks the dependence on the H4 tail. In addition, spacing activity has only been demonstrated on di-nucleosomal and tri-nucleosomal substrates. So, it is as yet unclear whether INO80 can generate large regular nucleosomal arrays, and whether this activity relates to its ability to exchange histone dimers as discussed above [20**].

New players in the DNA-damage response

Chromatin remodelling at DNA-damage sites is essential for repair machinery to access and correct DNA lesions, and it is also essential that chromatin structure is re-established after the repair process. Several Snf2-protein complexes have been identified as being involved in the DDR (Table 1). The most studied of these is the yeast INO80 complex [17]. Two mammalian Snf2 proteins have been newly identified as being specifically recruited to sites of DNA damage via poly (ADP-ribose) (PAR).

Alc1 (Amplified in Liver Cancer 1) is so-called as the *ALC1* gene is amplified in ~50% of hepatocellular carcinoma patients, and overexpression of Alc1 is oncogenic in mice [45]. Little is known about the molecular functions of Alc1, which consists of an N-terminal Snf2 domain and a C-terminal macrodomain, a known ADP-ribose binding module [46]. Two groups have shown Alc1 is recruited to sites of DNA damage and this recruitment is dependent on the macrodomain of Alc1, as well as PARP1, the major PARylating enzyme [47**,48**]. Furthermore, PARP1-mediated PARylation

Figure 3



Structural basis for allosteric regulation of the Snf2 domain from Chd1. In Chd1 (PDB ID: 3MWY) the two RecA lobes (blue and orange) of the Snf2 domain are splayed apart and stabilised in an open conformation by the chromodomains (green). This conformation is incompetent for ATP hydrolysis as RecA lobe 2 (orange) is not in contact with the ATP molecule (red). Structures of the related zebrafish Rad54 Snf2 domain (PDB ID: 1Z3I) and Vasa SF2 RNA helicase (PDB ID: 2DB3) in a closed ATPase competent conformation are shown for comparison. In these structures RecA lobe 1 and 2 are in close proximity and the ATP-binding pocket is buried between the two lobes (a red shadow can be seen through the surface). The chromodomains obscure a putative nucleic acid binding surface on lobe 2, the equivalent surface in Vasa, which is occupied by RNA (yellow), is circled. Binding of the chromodomains to a surface on the nucleosome is thought to release the Snf2 domain into an active state.

stimulates the nucleosome remodelling activity of Alc1, pointing to allosteric regulation of the Snf2 domain by PAR. Recruitment to DNA-damage sites is rapid and short-lived and requires catalytically active protein, suggesting that chromatin remodelling by Alc1 acts at an early stage in the DNA-repair pathway.

CHD4 (Chromodomain Helicase DNA-binding protein 4, also known as Mi-2 β) forms the Snf2-protein ATPase core of the NuRD (Nucleosome Remodelling and Deacetylase) complex and has been linked with both the repression and activation of gene expression [49]. Now, a series of studies have linked CHD4 with the DDR [50*,51,52*,53,54] and,

Table 1

Snf2-protein chromatin-remodelling complexes in the DNA-damage response (DDR)

Remodelling complex	Snf2-protein subunit	DDR-associated activities	Ref.
INO80	Ino80 (yeast)	Recruited via phospho-H2AX (γ -H2AX). Evicts nucleosome at damage sites. Participates in the DNA-damage cell cycle checkpoint pathway.	Reviewed in [17] and [55]
SWR1	Swr1 (yeast)	Recruited via γ -H2AX. Important for error-free non-homologous end-joining (NHEJ) pathway.	Reviewed in [17] and [55]
SWI/SNF	Snf2 (yeast) Brg1 or hBrm (human)	Associated with the homologous recombination (HR) repair pathway – possibly to clear nucleosomes and expose donor sequences to repair machinery. Human SWI/SNF facilitates γ -H2AX accumulation at DSBs.	Reviewed in [55]
RSC	Sth1 (yeast)	Linked with both HR and NHEJ repair pathways. May remodel DSB sites to facilitate loading of other repair factors.	Reviewed in [55]
Alc1	Alc1 (human)	Recruitment to damage sites by PARylation. Remodelling activity (<i>in vitro</i>) stimulated by PARylation of PARP1 and/or nucleosomes. Alc1-depletion leads to hypersensitivity to damaging agents.	[47**,48**]
NuRD	CHD4 (human)	Recruitment to damage sites by PARylation. CHD4 is phosphorylated by ATM kinase – a major DSB checkpoint kinase. CHD4-depletion leads to hypersensitivity to damaging agents and deficient DSB repair.	[50*,51,52*,53,54]
ACF	Snf2H (human)	ACF accumulates at sites of DNA damage. ATPase activity of Snf2H required for efficient DSB repair.	[56]

like Alc1, this link is dependent on PAR [50*,52*]. Depletion of CHD4 in human cells increases sensitivity to DNA damaging agents and is required for efficient double-strand break (DSB) repair [51,52*,53]. So far, a direct role for ATP-dependent chromatin remodelling by CHD4 at DNA-damage sites has not been shown, and it is possible the role of CHD4 is linked with other activities of the NuRD complex (such as deacetylation). However, direct binding to PAR can be mapped to the N-terminus of CHD4 [52*], so it will be intriguing to determine if its chromatin-remodelling activity is allosterically regulated by PAR binding, like Alc1.

Conclusions

It is becoming increasingly clear that Snf2 proteins and their complexes are required for diverse processes, and new discoveries regarding their actions will continue to emerge. As highlighted above, this is particularly evident in the DDR where numerous Snf2 proteins are being identified as having important roles. Many of these proteins are implicated in other processes, such as transcription, and it will be important to determine how their roles in these processes overlap and/or differ. The roles of some Snf2 proteins in genome-wide maintenance of variant nucleosomes make it attractive to consider whether they are global regulators of chromatin integrity rather than specific regulators of individual processes. In most instances it is poorly understood how the action of the Snf2 domain is tailored for specific roles. This is a challenging area of research as Snf2 proteins are multi-domain proteins with flexible regions and numerous interaction partners, and their substrates are complex. However, these challenges are being overcome by a combination of structural, kinetic, and functional analyses that are providing important new insights into the intimacy between Snf2 domains, accessibility domains, and substrate.

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