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REVIEW

Yeast chromatin remodeling complexes and their roles in transcription

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Abstract
The nucleosome is a small unit of chromatin, which is dynamic in eukaryotes. Chromatin conformation and post-translational modifications affect nucleosome dynamics under certain conditions, playing an important role in the epigenetic regulation of transcription, replication and reprogramming. The Snf2 remodeling family is one of the crucial remodeling complexes that tightly regulate chromatin structure and affect nucleosome dynamics. This family alters nucleosome positioning, exchanges histone variants, and assembles and disassembles nucleosomes at certain locations. Moreover, the Snf2 family, in conjunction with other co-factors, regulates gene expression in *Saccharomyces cerevisiae*. Here we first review recent findings on the Snf2 family remodeling complexes and then use some examples to illustrate the cooperation between different members of Snf2 family, and the cooperation between Snf2 family and other co-factors in gene regulation especially during transcription initiation.

Keywords Yeast · Histone nucleosome · Remodeling complex · Mediator · SAGA · Transcription

Chromatin remodeling and nucleosome dynamics

Within eukaryotic chromosomes, DNA is wrapped around proteins and hence protected from damage or unwinding under extreme conditions. This stable hereditary material also results in complicated gene regulation mechanisms unique to eukaryotes. Chromosomes further condense to form a more compact structure, named chromatin. Chromatin is the main configuration of hereditary material in eukaryotes during their cell interphase, and even some archaea contain chromatin-like substances. It is composed of several small units called nucleosomes. Nucleosomes consist of about 147-bp DNA wrapped around a core of eight histone proteins (the histone octamer) forming about 1.7 turns of a left-handed superhelix (Kornberg 1974). Eukaryotic cells typically contain five histone proteins, namely H1, H2A, H2B, H3 and H4. A pair of H2A-H2B and H3-H4 heterodimers comprise a core histone unit (Luger et al. 1997). Histone H1 binds to the linker DNA rather than being a part of the core particle, thus it is also called linker histone. The interaction between DNA and the nucleosome is not permanent but dynamic. This dynamic nature ensures that the nucleosome can be moved or become loosened from DNA to allow other proteins access to DNA (Watson et al. 2014), which is considered a key component for regulating expression of individual genes (Roberts and Orkin 2004). Chromatin remodeling caused by nucleosome dynamics is performed by two classes of multi-subunit complexes: one group of complexes can covalently modify histones or DNA, while another group uses the energy of ATP to mobilize nucleosomes. The latter group, called the ATP-dependent remodeling complexes, includes SWI/SNF (switching defective/sucrose nonfermenting) and RSC (remodels the structure of chromatin) complexes. This review mainly focuses on how complexes from this latter group regulate transcription initiation processes by changing the chromatin structure in yeast.

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The interaction between DNA and nucleosome proteins

Nucleosome proteins function to change dynamic interaction with DNA and play critical roles in gene regulation. Some of these proteins prefer to interact with DNA that is free from histones, so they can only recognize linker DNA, nucleosome-free region (NFR) DNA, or DNA that has been released from the histone octamer. Therefore, compared to binding sites that are near the end of nucleosomes (Fig. 1), binding sites located in the center of nucleosomes have less frequent access to the regulatory proteins (Watson et al. 2014).

The interaction between the histone octamer and DNA is influenced by nucleosome-remodeling complexes that contain an ATP-hydrolyzing DNA translocase subunit and include several families of proteins. There are several means by which these complexes mediate nucleosome changes. First, the histone octamer can slide along the DNA surface catalyzed by nucleosome-remodeling complexes, which is called "sliding" (Fig. 2a). One model of sliding suggests that the translocase subunit of the complex is placed adjacent to nucleosome DNA while other subunits tightly bind to the octamer. Then DNA moves along the surface of the histone octamer to generate a DNA loop, followed by propagation on the surface of the histone octamer until it reaches the end of the nucleosome DNA to complete sliding. Second, some nucleosome-remodeling complexes can catalyze the removal (eviction) of a nucleosome to expose the associated DNA (Fig. 2a). Third, some complexes can exchange a standard histone for a variant histone (Fig. 2a). For example, the replacement of H2A with H2A.Z by SWR1 (a Swi/Snf2-related adenosine triphosphatase), or H3 with H3.3 by CHD1 (chromodomain-helicase-DNA binding 1) remodeling complexes (Jiang and Pugh 2009). The variant histones H3.3 and H2A.Z are involved in the regulation of transcription (Henikoff and Smith 2015). Compared to standard histones, the variants have a few altered amino acids or added larger domains. Finally, some nucleosome remodeling complexes evenly space the distance between nucleosomes (spacing) (Fig. 2b). Meanwhile, some remodeling complexes can also cooperate with histone chaperones to wrap DNA around histone octamers to generate nucleosomes (deposition) (Fig. 2c). For instance, in budding yeast, histone chaperones Nap1 (nucleosome assembly protein) and Chz1 (chaperone for Htz1/H2A-H2B dimer 1) work in cooperation with the SWR1 complex to deposit H2A.Z into chromatin, during which Nap1 imports H2A.Z into the nucleus and Nap1 associated with Chz1 delivers H2A.Z to the Swr1 deposition machinery. Common histone chaperones in *S. cerevisiae* are summarized in Table 1.

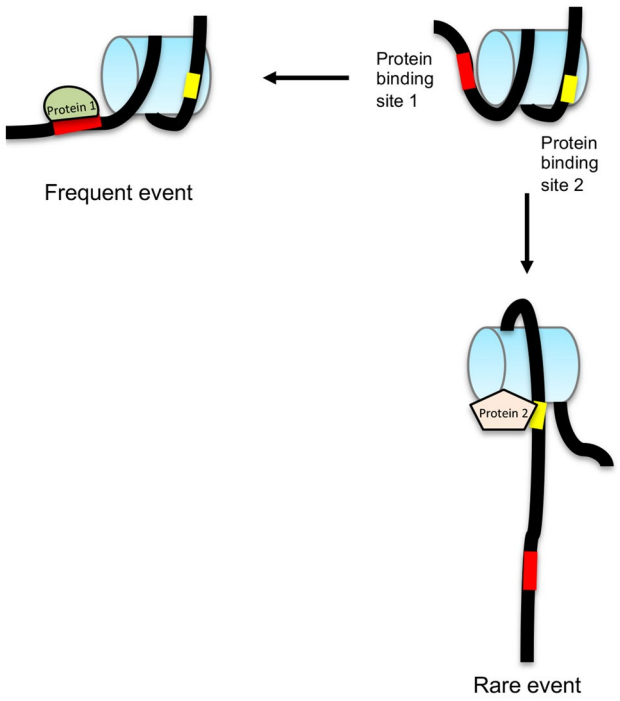

Fig. 1 The distinct incidences of DNA binding proteins in nucleosomes. Binding sites located at the regions that are free from histones are easily accessible by DNA binding proteins. In contrast, the binding sites occluded by histone octamers have fewer opportunities to interact with DNA binding proteins. The red spot (protein binding site 1) located at the end of the nucleosome has a much higher chance of binding to protein than the yellow site which is inside the nucleosome

Nucleosome-remodeling complexes

Chromatin/nucleosome-remodeling complexes are enzymes that use the energy from ATP hydrolysis to repose, evict, assemble or exchange histones and then affect DNA-based cellular processes, such as transcription, replication and DNA repair (Smolle 2018). The best-known remodeling complexes are SWI/SNF complexes originally found in yeast. Purified SWI/SNF complexes can disrupt nucleosome structure in an ATP-dependent manner. RSC, a second essential and abundant complex in yeast, bears orthologs to SWI/SNF subunits (Clapier and Cairns 2009). Brahma (brm) is a Swi2/Snf2 homolog found in *Drosophila melanogaster* (Kingston and Tamkun 2014), suggesting that similar complexes also exist in higher eukaryotes.

Members of the Snf2 family are characterized by certain signature motifs within the ATPase domain (Flaus et al. 2006), and the family is further divided into four subfamilies based on shared domains/motifs within their ATPase subunit, namely SWI/SNF2, ISWI, CHD and INO80 (Fig. 3), all of which are highly conserved from yeast to humans. These families differ in their requirements for

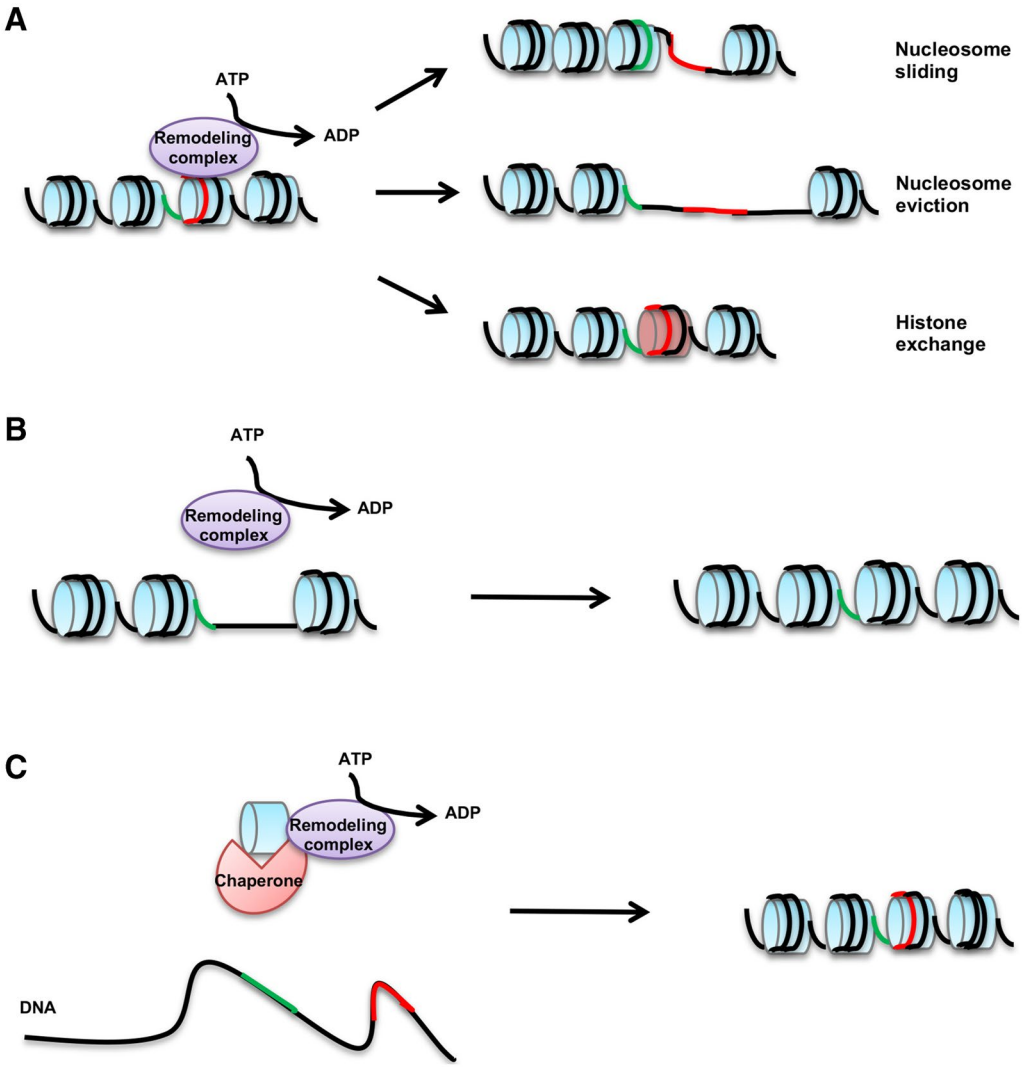

Fig. 2 The outcomes of chromatin remodeling by ATP-dependent remodeling complex. **a** The left side shows a starting chromatin structure, in which the green and red lines indicate linker DNA and nucleosomal DNA, respectively. The right side shows possible consequences of nucleosome movement: top, the nucleosome sliding to expose a region that has been previously occluded; middle, ejection of a nucleosome to expose the corresponding DNA; and bottom, the substitution of a standard nucleosome with a variant histone. **b** Some remodeling complexes equilibrate the irregular distance between nucleosomes, which is called nucleosome spacing. **c** Some histone chaperones collaborate with a remodeling complex to wrap DNA around histone octamers to form new nucleosomes

certain nucleosome elements during remodeling. For example, most ISWI remodelers require DNA flanking the nucleosome and the N-terminal tail of H4, whereas the SWI/SNF family does not have such requirements. Furthermore, some of these complexes, such as SWI/SNF, consist of a large number of proteins including up to 14 subunits, while others (such as ISWI and some CHD complexes) contain only one or a few additional subunits (Table 2). Despite these differences among families, they are all involved in transcription, DNA replication and DNA damage repair pathways (Clapier and Cairns 2009; Lans et al. 2012). We will first describe these four chromatin-remodeling subfamilies and then give some examples to illustrate their roles in transcriptional processes, particularly during transcription initiation.

SWI/SNF subfamily

The ATPase subunit of SWI/SNF subfamily contains an N-terminal HSA (helicase-SANT-associated) domain and a bromodomain, which can bind actin and/or actin-related proteins (ARPs) and recognize the acetylated lysine of histone and nonhistone proteins (Becker and Workman 2013). There are two similar SWI/SNF subtypes in yeast, RSC and SWI/SNF complexes (Carlson et al. 1984; Peterson and Herskowitz 1992). The SWI/SNF complex is dispensable, while the

Table 1 Histone chaperones in *S. cerevisiae*

Histone chaperone	Histone	Functions
Nap1 (Nucleosome assembly protein 1)	H2A-H2B, H2A.Z-H2B, H3-H4	Transcription
Chz1 (Chaperone for Htz1/H2A-H2Bdimer 1)	H2A-H2B, H2A.Z-H2B	Transcription
Asf1 (Anti-silencing function1)	H3-H4	Replication, repair, transcription
Vps75 (Vacuolar protein sorting 75)	H3-H4	Replication
Rtt106 (Regulator of Ty1 transposition 106)	H3-H4	Replication
Spt6 (Suppressor of Ty6)	H3-H4	Transcription
Spt16 (Suppressor of Ty 16)	H2A-H2B, H3-H4	Replication, repair, transcription
Cac1, Cac2 (Chromatin assembly complex 1, 2)	H3.1-H4	Replication, repair

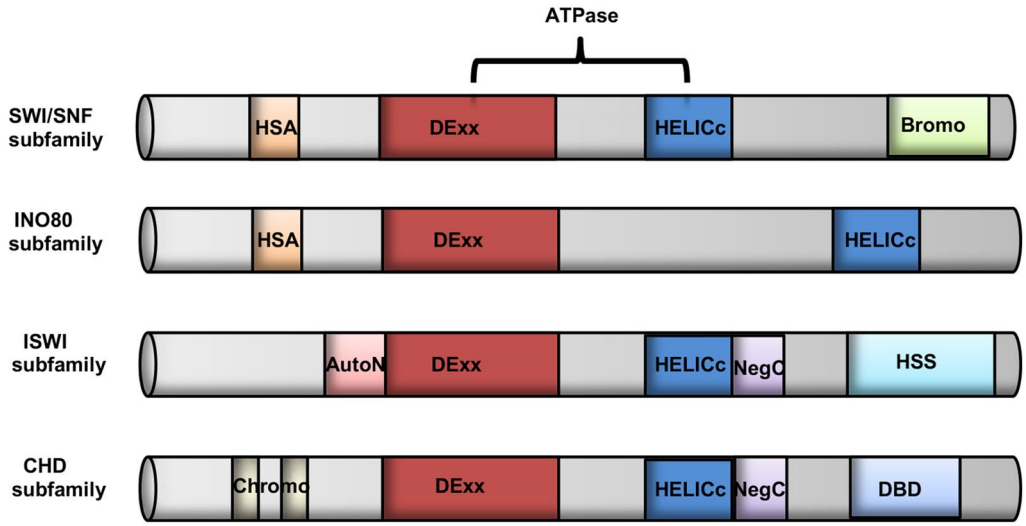

Fig. 3 Four subfamilies of Snf2 ATPase remodeling complex. The Snf2 family is identified by signature motifs within the ATPase domain and is further divided into four subfamilies, including SWI/SNF, INO80, ISWI and CHD, based on their additional domains. The SWI/SNF family contains HSA (helicase-SANT-associated domain) and a carboxy-terminal bromodomain. The INO80 family also contains a HSA domain, but it is further identified by a long insertion between the two ATPase subdomains. The ISWI family features a carboxy-terminal HSS (HAND-SANT-SLIDE) domain and two domains flanking the ATPase, namely AutoN (autoinhibitory N terminal) and NegC (negative regulator of coupling). The CHD family resembles ISWI remodelers that contain a C-terminal NegC and the analogue of HSS named DBD domain, but uniquely possesses tandemly-arranged chromodomains, which can bind methylated lysine of H3

RSC complex is essential for cell survival (Sundaramoorthy 2019). The counterparts of these two remodeling complexes in mammals are hBAF and hPBAF, and both are essential for cell survival (Sundaramoorthy 2019). Recent reports have shown that SWI/SNF and RSC play different roles in achieving wide NFRs for robust transcription at Gcn4-induced genes, and a strong cooperation between SWI/SNF and RSC is observed in nucleosome positioning and eviction at the most highly transcribed subset of constitutively-expressed genes in yeast (Rawal et al. 2018). SWI/SNF subfamily includes core subunits and several accessory subunits that have been reported to be involved in a variety of cancers (Masliah-Planchon et al. 2015; Zhang et al. 2018). In addition, this subfamily is crucial for chromatin access through nucleosome sliding and ejection, and is used for either target gene activation or repression (Clapier et al. 2017).

The SWI/SNF complex is highly conserved from yeasts to humans (Kasten et al. 2011; Zhang et al. 2018). Mutations in

Table 2 Subunit composition of Snf2 family chromatin remodeling complexes in *S.cerevisiae*

Sub-family	SWI/SNF		ISWI			INO80		CHD
In vivo functions	Transcription DNA replication DNA recombination		Transcription DNA replication DNA repair			Transcription DNA replication DNA damage responses		Transcription
Biological roles	Nucleosome sliding/ejection Histone exchange		Nucleosome assembly Nucleosome spacing			Nucleosome spacing Histone exchange		Nucleosome spacing Nucleosome ejection
Complexes	SWI/SNF	RSC*	ISW1a	ISW1b	ISW2	INO80	SWR1	CHD1
ATPase activity	Swi/Snf2	Sth1	Isw1 Isw1		Isw2	Ino80	Swr1	Chd1
Other subunits	Snf5 Swi3 Swi1 Snf6 Snf11 Arp9 Arp7 Swp73 Swp82 Rtt102 Taf14	Rsc8 Sfh1 Rsc6 Rsc2 Rsc4 Rsc7 Rsc9 Rsc3 Rsc30 Hst1 Rtt102 Rsc58 Arp9 Arp7	Ioc3	Ioc2 Ioc4	Itc1 Dph4 Dls1	Rvb1 Rvb2 Les1 Les2 Les3 Les4 Les5 Les6 Actin Arp4 Arp5 Arp8 Nhp10 Taf14	Rvb1 Rvb2 Swc2 Swc3 Swc4 Swc5 Swc6 Swc7 Actin Arp4 Arp6 Bdf1 Yaf9	

*The RSC complex subunit list is updated based on a recent study (Ye et al. 2019)

different genes that encode distinct subunits of the SWI/SNF complex, including Swi1, Swi2/Snf2 and Swi3, have been reported to impair induction of a variety of genes including *HO, INO1, ADH1, ADH2, SUC2, GAL1* and *GAL10* (Biggar and Crabtree 1999; Peterson and Herskowitz 1992; Sudarsanam et al. 1999). In addition to their involvement in transcriptional activation, SWI/SNF complexes also have been found to participate in repression. For example, SWI/SNF is involved in the repression of *SER3*, which encodes a phosphoglycerate dehydrogenase catalyzing a step in serine biosynthesis in *S. cerevisiae*, as *SER3* transcription increases more than 50-fold in the absence of Snf2. Compared to SWI/SNF activation, which needs several subunits, only the Snf2 subunit of SWI/SNF is strongly required for repression (Martens and Winston 2002). However, later studies indicate that the role of SWI/SNF repression is indirect since *SER3* repression depends on the increased expression of the noncoding *SRG1* gene (Ser3 regulatory gene), whose induction is required for SWI/SNF (Martens et al. 2005). Recently, it was reported that the SWI/SNF complex is involved in the regulation of *CTR1* expression. *CTR1* encodes a copper transporter and its expression is induced by a Mac 1 activator. SWI/SNF is essential for *CTR1* transcription in association with Mac1, Ssn6 and Hir1, by which SWI/SNF is recruited to the *CTR1* promoter by both Mac1 and Hir1 to initiate a positive feedback loop for further recruitment of Mac1, Hir1 and SWI/SNF, whereas Ssn6 serves as a rpressor (Voutsina et al. 2019).

The RSC complex is associated preferentially with promoters and intergenic regions, and is specifically recruited to RNA polymerase II to activate transcription, or to repress transcription in some circumstances (Lorch and Kornberg 2015). Depletion of RSC leads to a marked diminution in the size of NFRs genome-wide in yeast (Hartley and Madhani 2009), suggesting that RSC is involved in the formation of NRFs. In addition, two studies have demonstrated that RSC is associated with a perturbation of structure of the + 1 nucleosome to regulate transcription (Ramachandran et al. 2015; Rhee et al. 2014). For example, gene regulatory and TATA-box (or TATA-like) sequences are exposed by RSC in an ATP-dependent manner and then RSC binds the adjacent + 1 nucleosome, which contains the transcription start site(s), to partially unwrap the nucleosomal DNA. Subsequently, an activator may bind to a regulatory element to remove the + 1 nucleosome and initiate transcription (Lorch and Kornberg 2015).

Low-resolution cryo-EM (electron microscopy) structure showed that SWI/SNF family proteins are globular, C-shaped with a central cavity or depression, in which the nucleosome can be accommodated (Lorch and Kornberg 2015). A ~ 4.5 Å resolution cryo-EM structure of a minimal fragment of the Snf2 ATPase core domain in complex with nucleosome showed that the Snf2 fragment binds the nucleosome at two different locations (Liu et al. 2017). The first is SHL2 (superhelical location 2), which is proximal to the linker DNA; the second one is SHL-6, which is at the edge of the nucleosome. The H4 tail is the only histone contact found between the Snf2 fragment and the nucleosome, and is bound at the conserved acidic patch on lobe2 of the ATPase (aa16–19) (Liu et al. 2017). Snf2 is in an

open conformation upon ADP binding and generates a 1-bp bulge at SHL2 location; once binding ATP, Snf2 becomes a closed conformation, during which lob2 (DExx, lobe1; HELICc, lobe2) will grips the DNA strand and pushes the 1-bp DNA toward the exit side to complete DNA translocation (Yan and Chen 2020). However, questions like how the enzymes are targeted to specific nucleosomes remain to be answered by high-resolution structures of the complete SWI-SNF complex in the future. In addition, a crystal structure of RSC Sth1 and a series of experiments demonstrated that auxiliary subunits such as Arp7, Arp9 and Rtt102 fine-tune the ATPase for productive remodeling (Clapier et al. 2016).

INO80 subfamily

A notable feature of the ATPase subunit of INO80 (inositol-requiring mutant 80) subfamily is a variable, large insertion (~250 amino acids in yeast) between two ATPase subdomains, which binds to a single heterohexameric ring of the helicase-related RuvB-like protein Rvb1/2 (Clapier et al. 2017); it also contains an N-terminal HSA domain. This subfamily includes two members, INO80 and SWR1, named after their key ATPase subunits Ino80 and Swr1.

The INO80 complex contains 15 subunits, which include four structurally different and biochemically separable subunit modules in yeast (Tosi et al. 2013; Watanabe et al. 2015), while the SWR1 complex contains 14 subunits. INO80 complexes have been reported to regulate transcription, replication, DNA damage responses and mitotic stability (Morrison 2017; Zimmer and Fabre 2019), and different functions for their subunits have been identified by yeast genetic analyses (Morrison 2017).

Both INO80 and SWR1 complexes exhibit unique editing functions (histone exchange activity), but only the INO80 complex conducts nucleosome-sliding activity (Brahma et al. 2017). Swr1 exchanges H2A to H2A.Z in the nucleosomal H2A/H2B dimer without causing net DNA translocation, and it is conceivable that local DNA translocation induced by Swr1 generates a loop between the two binds sites (SHL6 and SHL2), resulting in loss of the H2A-H2B dimer-DNA contacts to promote dimer exchang transloction (Yan and Chen 2020). Genome-wide studies have demonstrated that H2A.Z is globally localized to most of the promoters, especially highly enriched at the + 1 and − 1 nucleosome positions in euchromatin, and plays an important role in transcriptional activation or repression in yeast (Guillemette et al. 2005; Raisner et al. 2005; Raisner and Madhani 2006; Zhang et al. 2005). In contrast, Ino80 promotes the opposite dimer exchange reaction (Papamichos-Chronakis et al. 2011), exchanging H2A.Z to H2A. In addition, a different approach is used by the INO80 complex to exchange the H2A.Z-H2B dimer: exchange of the H2A.Z-H2B dimer is conducted by nucleosome interactions and translocation of the Ino80 ATPase, which uses DNA twist and torsional strain to move DNA around the nucleosome and to exchange the H2A.Z-H2B dimer for H2A-H2B (Brahma et al. 2017). In addition to histone exchange, the INO80 complex also conducts sliding activity. Recently, it was shown that the INO80 complex is the only remodeler that is sufficient for positioning the + 1 nucleosome at the promoters of in vitro-reconstituted yeast chromatin (Krietenstein et al. 2016), suggesting that the sliding activity of INO80 plays an important role in positioning nucleosomes, especially the + 1 nucleosome (Zhou et al. 2018). Yeast INO80 complex has also been reported to slide mononucleosomes toward the center of a short DNA (Udugama et al. 2011). The INO80 complex exhibits a switch-like response to flanking DNA for nucleosome sliding, which requires at least ~ 50 bps of flanking DNA for efficient sliding (Zhou et al. 2018). Meanwhile, the Nhp10 module of the INO80 complex inhibits the remodeling of nucleosomes with short flanking DNA without affecting ATPase rates (Zhou et al. 2018). The above observations suggest that although both SWR1 and INO80 complexes belong to the INO80 subfamily, they have different functions. For example, SWR1 and INO80 play distinct roles in transcription, as INO80 possesses multiple functions, whereas SWR1 is specialized for H2A.Z exchange (Brahma et al. 2017; Gerhold and Gasser 2014; Gerhold et al. 2015). In addition, a histone chaperone is required for the H2A.Z incorporation by SWR1; however, no histone chaperone has been found for INO80 functions so far. Furthermore, structural studies have shown that INO80 and SWR1 interact differently with nucleosomes (Brahma et al. 2017; Gerhold and Gasser 2014). For instance, Swr1 binds at the internal sites SHL2 and SHL6 of the nucleosome. In contrast, Ino80 binds at the SHL6/7 position (Sundaramoorthy 2019).

INO80 and SWR1 complexes still bear some similarities in their assembly even though they interact differently with nucleosomes. High resolution EM reconstructions of both INO80 and SWR1 complexes showed that they contain a similar Rvb hetero-hexamer (Sundaramoorthy 2019; Tosi et al. 2013), which serves as a scaffold to allow other subunits to be assembled. In both complexes, the insert of Ino80/Swr1 forms a planar structure to contact every single Rvb promoter, while ATPase lobe2 of these two complexes also forms an additional close interaction with the Rvb hexamer. In addition, the Arp5/Ies6 heterodimer in INO80 and the Arp6/Swc6 heterodimer in SWR1 interact with the Rvb hexamer.

ISWI subfamily

The ISWI (Imitation SWItch) subfamily was first discovered in *Drosophila* (Tsukiyama et al. 1995; Varga-Weisz et al. 1997). The ATPase subunit of this subfamily features a carboxy-terminal HAND-SANT-SLIDE (HSS) domain

that binds the unmodified histone H3 tail and the linker DNA flanking the nucleosome. Two domains, autoinhibitory N terminal (AutoN) and negative regulator of coupling (NegC), flank the ATPase domain to regulate its activity. The remodeling activity is reduced if either the SANT or SLIDE domain is deleted in yeast (Grune et al. 2003; Hota et al. 2013; Mueller-Planitz et al. 2013), especially in the case of the SLIDE domain because it interacts with extra-nucleosomal DNA to stimulate ATPase activity and is required to move DNA along the nucleosome. ISWI subfamily complexes are relatively small in size and contain only a few subunits, but most of them can assemble and regularly space nucleosomes to limit chromatin accessibility and gene expression (Clapier et al. 2017; Kagalwala et al. 2004). In budding yeast, there are two members of ISWI: Isw1 and Isw2, which can form three distinct complexes (Kagalwala et al. 2004; Vary et al. 2003). Isw1a and Isw1b are two separate complexes that contain Isw1: Isw1a contains Ioc3, while Isw1b contains Ioc2 and Ioc4 (Mellor and Morillon 2004). The two complexes have equivalent nucleosome-stimulated ATPase activities and overlapping functions in transcriptional regulation of some genes, but differ in their abilities to bind to DNA and nucleosomal substrates (Morillon et al. 2003; Vary et al. 2003); Isw1 can either repress or promote transcription depending on the proteins with which it is in contact. For example, the repression of *PHO8* requires Isw1 and appears to be mediated by displacement of TBP from the promoter that is also dependent on the transcription factor Cbf1 (Mellor and Morillon 2004). Similar regulation by Isw1 was also observed at the *MET16* promoter: after Isw1 enrichment, the Isw1 ATPase positions nucleosomes − 1 and + 1 associated with the promoter region (Morillon et al. 2003), from which increased levels of trimethylation at K4 of histone H3 were observed. It was also reported that modifications of histone H4 influence Isw1-mediated silencing of *MET16* (Morillon et al. 2003). Compared to Isw1, Isw2 mainly represses gene expression by positioning nucleosomes to inhibit transcription. Isw2 is reported to form a heterodimer with Itc1, which is recruited to promoters of several early meiotic genes by Ume6 to repress expression during vegetative growth (Goldmark et al. 2000; Whitehouse et al. 2007). Strains lacking Ume6 show changes in nucleosome position similar to those observed in an *isw2* strain (Kent et al. 2001). Lately, two new subunits of the Isw2 complex, Dpb4 and Dls1, were identified in *S. cerevisiae* (McConnell et al. 2004). Isw2 is reported to cooperate with histone deacetylation to forbid TBP binding at some target promoters, such as *HOP1* (Shimizu et al. 2003).

The biochemical analysis and crystal structure at 2.4 Å have characterized the ISWI ATPase relatively well. The HSS domain, which is located at the C-terminal region of ATPase, functions in binding extra-nucleosomal DNA. The AutoN domain inhibits ISWI activity by bridging lobe1 and lobe2 of ATPase (DExx, lobe1; HELICc, lobe2), while the H4 tail can release the inhibition by competitive binding to lobe2. Acetylation of H4 tail, which can weaken the H4-ISWI interaction, attenuates ISWI activation (Yan and Chen 2020). In addition, the C-terminal NegC domain inhibits DNA translocation, which can be released upon the binding of NegC to extra-nucleosomal DNA (Sundaramoorthy 2019). The DNA translocation mechanism mediated by ISWI remains controversial between NMR and cryo-EM structures, although cryo-EM structures of the ISWI-nucleosome complex imply a similar DNA translocation mechanism between ISWI and Snf2 (Yan and Chen 2020). X-ray crystallographic and EM reconstruction of the nucleosome spacing module (HSS domain and Ioc2) of the yeast ISW1a show that it binds to two types of nucleosomes with different linkers (Yamada et al. 2011), suggesting that one ISWI remodeler simultaneously interacts with two adjoining nucleosomes to regulate their spacing. High-resolution structural reconstruction of the full ISWI remodeler binding nucleosome will further elucidate the details of this family (Sundaramoorthy 2019).

CHD subfamily

The ATPase subunit of the CHD (chromodomain-helicase-DNA binding) subfamily resembles ISWI remodelers, but uniquely bears tandemly-arranged chromodomains that can recognize and bind methylated lysine residues of histone H3 (Becker and Workman 2013). Analogous to ISWI, CHD remodelers contain a C-terminal NegC domain (Singleton et al. 2007), followed by a DNA-binding domain (DBD) comprised of only SANT and SLIDE motifs (Ryan et al. 2011). The CHD subfamily can be further divided into three subfamilies according to the presence of additional structural motifs (Hall and Georgel 2007; Marfella and Imbalzano 2007), of which Chd1 belongs to the first CHD subfamily and is the only CHD family member present in *S. cerevisiae*. Chd1 is a highly conserved remodeler and functions as a monomer, unlike most other remodelers that form multi-subunit enzyme complexes (Marfella and Imbalzano 2007). Chd1 deposits histones onto DNA, generates regularly spaced arrays together with histone chaperones and promotes the movement of histones away from bound transcription factors in vitro (Lusser et al. 2005; Nodelman et al. 2016). Chd1 is also recruited to RNA polymerase II on actively transcribed genes with the PAF complex (Lee et al. 2017) to ensure the recycling of histones during transcription and to limit the incorporation of soluble, highly acetylated histones associated with open chromatin (Smolle 2018). yFACT (facilitate chromatin transcription) was first identified as a factor promoting RNA polymerase II transcription in vitro using assembled chromatin as a template (Biswas et al. 2007). Deletion of *CHD1* suppresses growth

defects of yFACT mutant strains including *spt16* and *pob3* mutations and suppresses synthetic lethality between *spt16* and other transcription factors such as *isw1*, *isw2*, *nhp6* and *htz1*. These observations suggest that Chd1 has opposing roles in regulating transcription with yFACT (Biswas et al. 2007). Recently, an additional C-terminal CHCT domain has been identified in Chd1. The highly conserved CHCT domain binds to both DNA and nucleosome in vitro (Mohanty et al. 2016).

At present, two resolved high-resolution EM structures have provided more details about the architecture of the nucleosome-bound Chd1 structure, revealing that Chd1 binds to nucleosomes and generats a twisted DNA translocation in ADP-bound states in a manner similar to Snf2 (Farnung et al. 2017; Sundaramoorthy 2019; Sundaramoorthy et al. 2018). The DBD binds to the linker DNA, while the ATPase domains bind to the SHL2 location of the nucleosome, which is in closest proximity to the DBD but is distal to the linker DNA (Sundaramoorthy 2019). Thus the Chd1 binding results in two turns of entry side of the nucleosomal DNA unwrapping from the surface of the histone core, whose extent is related to inter-domain communications (Sundaramoorthy 2019; Sundaramoorthy et al. 2018). The resolved Chd1-nucleosome complex structure also shows that the H4 tail binds to the Chd1 ATPase lobe2 at a conserved acidic patch that plays a critical role in the Chd1 activity. In addition, the interaction between H3 and Chd1 is also important for Chd1 activity (Sundaramoorthy 2019). However, further studies are still required to explain how Chd1 centers the end-positioned nucleosome towards the center of a DNA fragment.

Chromatin remodeling and transcription initiation

Transcription initiation at promoters

Transcription activation is a multistage process including initiation, elongation and termination. In this review we focus on the initiation step. Transcription activation begins with the removal of repressors from the promoter to initiate transcription, followed by the activator binding to the core promoter (including the TATA box and transcription start site), which leads to the recruitment of co-activator complexes such as Mediator or SAGA (Shetty and Lopes 2010). General transcription factors (GTF) are recruited at the next step and Pol II is recruited by TFIID, TFIIA and TFIIB to form the preinitiation complexes (PIC) at the core promoter region. Finally, RNA synthesis begins with the help of TFIIH. The carboxy-terminal domain (CTD) of Pol II is phosphorylated by TFIIH at the beginning of transcription and loses its contacts with the GTFs before it proceeds on to the elongation stage. At the same time, the phosphorylated CTD begins to recruit elongation and mRNA processing factors.

Two promoter classes and nucleosome occupation in yeast

Budding yeast contains two classes of promoters based on nucleosome occupancy: open and covered (Cairns 2009; Tirosh and Barkai 2008). Open promoters have NFRs located immediately upstream of the transcriptional start site. The NFR region provides the binding site for a transcription factor and initiates assembly of the PIC. Such promoters regulate expression of constitutive and housekeeping genes. In contrast, the NFRs in covered promoters are relatively short and the sites for PIC assembly and other binding sites for transcription factors are usually covered by nucleosomes. Such promoters regulate inducible or stress-responsive genes and rely on chromatin co-factors such as nucleosome remodeling complexes for their activation. Compared to genes with open promoters that exhibit settled NFR, most stress-responsive genes have no stereotypic nucleosome arrangements and appear to have more variable promoter architecture (Ioshikhes et al. 2006). Importantly, transcription factor-binding sites at these covered promoters are usually occluded by nucleosomes; rapid changes of nucleosomes expose the binding sites under different stress conditions (Tirosh and Barkai 2008). Covered promoters are important models for gene regulation through switching chromatin states: the *PHO* promoters establish basic principles of regulation by chromatin. For example, the *PHO5* gene has a covered promoter and is one of the first established models for gene regulation through chromatin remodeling complexes (Rando and Winston 2012). Three upstream activation sequences can activate *PHO5* transcription, including UASp1 (UAS1), UASp2 (UAS2) and the TATA box. The TATA region and UASp2 are wrapped into nucleosomes N-2 and N-1, while UASp1 is not wrapped but surrounded by nucleosomes N-3 and N-2; therefore all three *PHO5* UASs are inaccessible under normal conditions. Upon *PHO5* activation, nucleosomes N-3 and N-2 are removed, and nucleosome N-1 is also relocated from the promoter site to the gene coding site to release all three UASs, as shown in Fig. 4.

Normally, the first nucleosome upstream of the 5′ NFR is the − 1 nucleosome, while the first nucleosome downstream of NFR is the + 1 nucleosome. In the *S. cerevisiae* genome, the first critical nucleosome for transcription initiation is the -1 position that is located upstream of the transcription start site (TSS) and covers a region from − 300 to − 150 relative to the TSS to regulate the accessibility of promoter regulatory elements in this region. The − 1 nucleosome undergoes many changes including histone replacement, repositioning

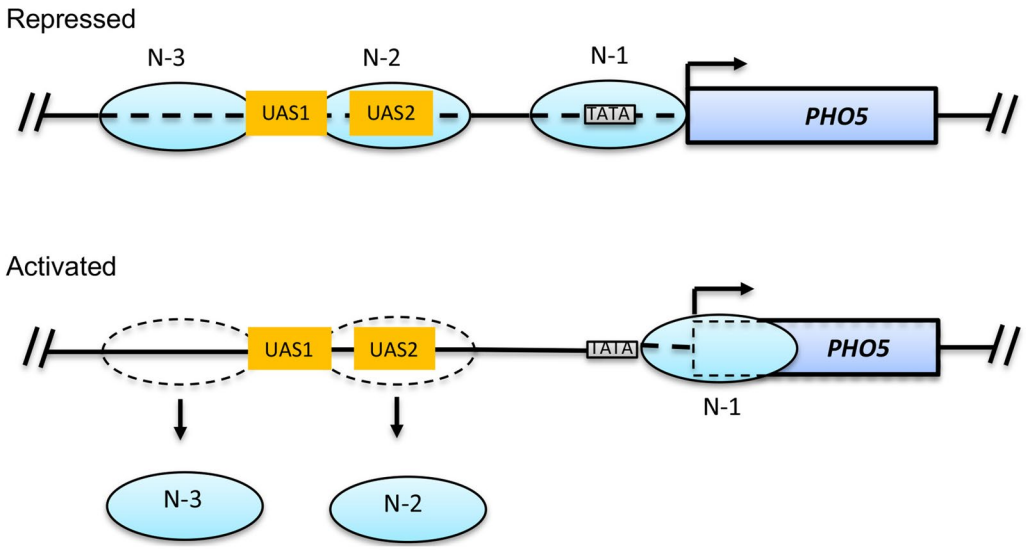

Fig. 4 The nucleosome landscape of the *PHO5* covered promoter in yeast. In the repressed state, the upstream activation sequence UAS2 and the TATA region of *PHO5* are wrapped into nucleosomes N-2 and N-1, while UAS1 is not wrapped but surrounded by nucleosomes N-3 and N-2. Once *PHO5* is activated, N-2 and N-3 are removed, and N-1 moves towards the gene coding site to expose all three upstream activation sequences to initiate transcription

and modification, to affect gene expression during transcription. The + 1 nucleosome usually contains histone variants (H2A.Z and H3.3) and histone tail modifications (e.g., methylation and acetylation) (Cosgrove and Wolberger 2005; Kouzarides 2007; Li et al. 2007; Malik and Henikoff 2003).

Altered transcription is correlated to changes in the chromatin structure caused by nucleosome dynamics (Jiang and Pugh 2009). Most of these changes in chromatin structure are caused by chromatin-remodeling factors that are recruited by transcription factors or RNA polymerase II (RNAPII). However, Snf2 family chromatin-remodeling complexes play roles in gene activation not only by themselves but also through cooperation with other co-factor complexes. Here, we summarize cooperation between Snf2 family remodelers and some co-activators such as SAGA and Mediators.

Cooperation between remodeling complexes and other co-activators at promoters

Co-factors are transcription factors that themselves cannot interact with DNA but are indispensable for transcriptional activation in coordination with other transcription factors. Chromatin remodeling complexes, such as those in the Snf2 family, are special types of co-factors (Shetty and Lopes 2010). Some cooperation between Snf2 family chromatin remodeler complexes and other co-activators, such as SAGA and Mediator, are involved in activation and initiation at promoter regions.

Cooperation among SWI/SNF complex, SAGA and mediator

A well-studied cooperation between the chromatin remodeling complex and other co-factors is the SWI/SNF complex and SAGA (Spt-Ada-Gcn5-acetyltransferase complex). The recruitment of SAGA has been associated with recruitment of the SWI/SNF complex in many instances (Gregory et al. 1999; Hassan et al. 2001, 2002; Syntichaki et al. 2000). For example, both the ATP-dependent nucleosome remodeling activity of the SWI/SNF and the histone acetylation activity of the SAGA complex are required for chromatin remodeling at the *PHO8* promoter, although they have different effects on the chromatin remodeling in vivo (Gregory et al. 1999).

Activation of *ADE* genes also requires both SAGA and SWI/SNF complexes. *ADE* genes encode enzymes of the purine nucleotide biosynthetic pathway in *S. cerevisiae* and are transcriptionally repressed when cells are cultured in the presence of purine bases such as adenine. Transcription factors Bas1 and Pho2 are involved in up-regulation of nine *ADE* genes under derepressing conditions (Daignan-Fornier and Fink 1992; Zhang et al. 1997). The catalytic activities of SAGA and SWI/SNF are required for activation of *ADE* genes, through affecting the occupancy of Bas1 and Pho2 at the *ADE* promoter region but not their expression (Koehler et al. 2007). In addition, the *gcn5 snf2* double mutant shows much more sensitivity than its corresponding single mutants, suggesting additive roles of SAGA and SWI/SNF remodeling activities at the *ADE* genes (Koehler et al. 2007). All these results show that SAGA and SWI/SNF function together as co-activators in *ADE* gene derepression.

Ansari et al. (2014) demonstrated the interdependency of co-activator complex recruitment during transcription initiation at the *CHA1* promoter in yeast. They found dependence on SWI/SNF recruitment on the Mediator tail module at the induced *CHA1* promoter. Mediator comprises 25 subunits (Table 3) in *S. cerevisiae* and can be roughly divided into four domains including the tail, middle, head and cyclin-CDK modules (Lariviere et al. 2012). Recruitment of the SWI/SNF complex also depends on Mediator at constitutively active genes, for which SWI/SNF loss does not affect histone occupancy (Ansari et al. 2014). However, the commonalities and promoter-specific features of interdependence of co-activator complex associations remain to be elucidated.

The SWI/SNF remodeling complex also functions together with both SAGA and Mediator at certain promoters. The SWI/SNF complex has been reported to be involved in the transcriptional activation of a number of diversely regulated genes such as *INO1*, *SUC2* and *HO*. *HO* encodes an endonuclease to initiate mating type inter-conversion in budding yeast (Strathern et al. 1982). The initiating event of *HO* activation needs the binding of Swi5 to URS1 (upstream repression sequence 1), followed by Swi5 recruitment of three co-activator complexes including SWI/SNF, SAGA and Mediator. SWI/SNF remodeling nucleosomes proceed as a cascade of nucleosome evictions, starting from URS1 to the right half of URS2, to allow SBF (the SCB binding factor) to bind to its sites within URS2. SBF can also recruit SWI/SNF, SAGA and Mediator to extend nucleosome eviction to the TATA region, thus allowing association of RNA polymerase to initiate transcription (Parnell and Stillman 2019). Another example is the *ACR2/3* gene: Yap8 is an activator of *ACR2* and *ACR3* genes, which are involved in the response to arsenic stress in *S. cerevisiae* (Menezes et al. 2004). A tail subunit of the Mediator complex Med2 functions as a Yap8 interaction partner, suggesting that Mediator is a co-regulator to act as a bridge between Yap8 and the core transcription machinery (Menezes et al. 2017). However, Mediator is not the only co-activator sustaining transcriptional activation of *ACR2* and *ACR3* genes by Yap8; SWI/SNF and SAGA complexes are also involved: lack of SWI/SNF subunits Snf2 or Snf5 diminishes Yap8 access to the *ACR2/ACR3* promoter and impairs *ACR2* up-regulation (Menezes et al. 2017). Ablation of Spt20, which is a subunit of SAGA, reduces Yap8 occupancy at the *ACR2/ACR3* promoter and renders cells sensitive to arsenate stress, suggesting that SAGA activities are also required to express Yap8-mediated *ACR2* (Menezes et al. 2017). In this example, Yap8 interacts with Mediator through the tail subunit Med2 and recruits SWI/SNF remodeling and SAGA complexes to support proper arsenic adaptation and full *ACR2/3* activation.

Besides SWI/SNF, other remodeling complexes such as SWR1 also work together with other co-factors to regulate initiation of transcription. The SWR1 complex contains fourteen subunits (Table 2), among which Swr1 is the key catalytic subunit crucial for its function (Mizuguchi et al. 2004). Some other subunits, such as Swc4, Arp4, actin and Yaf9, are also present in the NuA4 histone acetyltransferase complex that can acetylate H2A.Z, indicating a functional correlation between SWR1 and NuA4 complexes (Doyon and Cote 2004; Shen et al. 2000). Later, a model for H2A.Z deposition by these two complexes was proposed: Bdf1, the shared component of SWR1 and TFIID complexes, recognizes a specific histone acetylation site and recruits the SWR1 complex to specific loci in the genome and then the canonical H2A-H2B dimers are exchanged for H2A.Z-H2B through the remodeling activity of the SWR1 complex. The NuA4 complex is recruited by the shared subunits of SWR1 and NuA4 complexes, which further acetylates the deposited H2A.Z. The modified H2A.Z further functions in transcriptional activation, antagonization of gene-silencing or chromosome stability (Bao and Shen 2007).

All of the above observations imply that transcriptional initiation requires a limited set of co-activator complexes to function at promoters to regulate gene expression.

Cooperation between Snf2 family remodeling complexes

The Snf2 family not only works with other co-factors but also cooperates with its different subfamily members. The yeast gene *INO1* (inositol-3-phosphate synthase), which is repressed by inositol and choline and completely derepressed in their absence (Shetty and Lopes 2010), encodes a key enzyme required for the de novo synthesis of

Table 3 Subunit composition of the *S. cerevisiae* Mediator

Backbone/scaffold	Head	Middle	Tail	Cyclin-CDK
Med14/Pgr1	Med6	Med1	Med2	Med12/Srb8
	Med8	Med4	Med3/Pgd1/Hrs1	Med13/Srb9/Ssn2
	Med11	Med7	Med5/Nut1	Cdk8/Srb10/Ssn3/Ume5
	Med17/Srb4	Med9/Cse2	Med15/Gal11	CycC/Srb11/Ssn8/Ume3
	Med18/Srb5	Mde10/Nut2	Med16/Sin4	
	Med20/Srb2	Med19/Rox3		
	Med22/Srb6	Med21/Srb7		
		Med31/Soh1		

phosphatidylinositol from glucose-6-phosphate. The regulation of *INO1* involves both SWI/SNF and INO80 remodeling complexes, which lead to chromatin remodeling at the promoter region (Ford et al. 2007). Both SWI/SNF and INO80 are present at the *INO1* promoter prior to, but not after induction. In addition, Ino2, the activator of *INO1*, is required to recruit these two complexes to the promoter region, as evidenced by the fact that both of them are absent from the *INO1* promoter in the *ino2*Δ strain. Interestingly, the Ino2-dependent recruitment of INO80 is necessary for the SWI/SNF recruitment but the INO80 recruitment is SWI/SNF independent (Ford et al. 2008). Based on the above observations, a working model for transcriptional activation of *INO1* chromatin was proposed (Ford et al. 2008) to explain the detailed mechanism of how more than one remodeling complex work together for gene induction in an activator-dependent manner. A similar finding was also observed for *HIS3* (Kim et al. 2006), suggesting that such an activation pathway involving different remodeling complexes during gene induction is not unique. Later, ISWI family remodeling proteins were shown to be involved in the repression of *INO1* expression (Mellor and Morillon 2004; Ocampo et al. 2016; Sugiyama and Nikawa 2001). However, the ISW2 complex was also found to be required for complete *INO1* derepression and is recruited by an interaction with the Ino2-Ino4 heterodimer, which also requires another DNA binding protein, CBF1 (Shetty and Lopes 2010). A model involving Cbf1 and ISW2 to regulate *INO1* transcription was proposed in which the ISW2 complex remodels chromatin in the *INO1* promoter through interaction with the Ino2-Ino4 heterodimer in a Cbf1-dependent manner (Shetty and Lopes 2010). *ADH2* provides another example: it was reported that removing Chd1 or Isw1 remodeling factors delays the high-level expression of *ADH2*, suggesting that Chd1 and Isw1 play a role in the regulation of *ADH2* expression, although the promoter structure of *ADH2* is not changed by Chd1 complexes (Xella et al. 2006).

In addition to cooperation, the competition among different remodelers at promoter regions was also observed, and the authors proposed that CHD1 competes with ISW1 to determine nucleosome spacing on most yeast genes, with CHD1 forming short-spaced nucleosomal arrays and ISW1 converting these arrays to longer spacing (Ocampo et al. 2016).

Conclusions and future directions

This review summarizes our current understanding on how chromatin remodeling complexes affect gene expression in yeast, particularly at the transcription initiation step. Chromatin remodeling complexes can regulate transcription by several means, including nucleosome sliding, histone exchange, histone eviction, nucleosome deposition and spacing. A single chromatin remodeling complex can use different means to alter chromatin structure; for example, the SWI/SNF subfamily can both slide and evict nucleosomes during transcription, whereas the INO80 complex not only has histone exchange activity but also nucleosome sliding activity at the cognate promoters. Although these remodeling complexes are multi-functional, they usually act together with other co-factors that are recruited by activators or repressors, or interact with general transcriptional factors to regulate gene expression in yeast. A well-studied cooperation is among SWI/SNF, SAGA and Mediator, for which some examples have been illustrated. However, experiments are still largely limited to determine whether a co-activator protein or complex is necessary for activating and maintaining the transcription activation of certain genes, as mechanistic details are still elusive. For instance, SWI/SNF, SAGA and Mediator are involved in the transcriptional activation of *ACR2* and *ACR3* genes by Yap8 since some subunit mutants of these complexes were sensitive to arsenate. However, how SAGA and SWI/SNF are recruited to the *ACR2/3* promoter and how these three co-activator complexes work with Yap8 to regulate *ACR2/3* transcription under arsenate stress remain to be further investigated.

Transcriptional activation or regulation is a complex, multistep process implemented by hundreds of proteins, in which co-factor complexes function with transcriptional activators or repressors at numerous genes. The large number of factors and multiple functions of co-factors lead to the complexity and variability of mechanisms of gene regulation. Future research may reveal more details of the interplay between chromatin remodeling complexes and other transcriptional factors and among different remodelers to dynamically remodel chromatin states and transcription, especially under stress conditions.

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