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ATP-dependent Chromatin Remodeling Enzymes and their Various Roles in Cell Cycle Control

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1. ABSTRACT

The modification of chromatin structure by various mechanisms has emerged as a key regulatory component of nuclear programs. Cell cycle progression and exit are affected by the integrity of chromatin architecture as well as by regulatory cues that chromatin structure imposes on the expression of cell cycle genes. ATP-dependent chromatin remodeling factors use the energy derived from ATP-hydrolysis to modulate histone-DNA contacts. These molecular machines play important roles in all aspects of chromosome biology and are thus intimately linked to cell cycle control. Regulation of complex activity by various signaling pathways has been a rising theme in recent years. Moreover, some chromatin remodeling factors have been characterized as potent tumor suppressor proteins. Thus, to understand the functions and activities of ATP-utilizing chromatin remodeling factors is an important goal towards their use as potential targets in cancer therapy.

2. INTRODUCTION

In eukaryotes, DNA and the histone proteins H2A, H2B, H3, H4 associate to form the nucleosome, which is the basic building block of chromatin. Chromatin not only functions to compact the genetic material but also contributes to the regulation of nuclear processes. Different strategies have evolved by which chromatin architecture can be modulated in the course of transcription, replication, recombination or repair. For instance, posttranslational covalent modifications of histones alter the biochemical properties of chromatin as well as generate signals that specify the functional state of a genomic region (1-4). Histone variants and non-histone chromosomal proteins are incorporated to modify the structure and activity of chromatin (5-8). Moreover, ATP-powered molecular machines known as chromatin remodeling factors serve to modify chromatin structure by modulating histone-DNA contacts. Their action results in repositioning, removal or

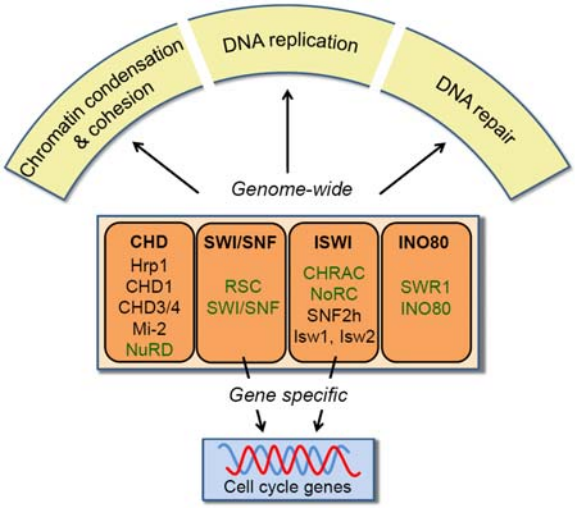

Figure 1. ATP-dependent chromatin remodeling factors affect cell cycle regulation at multiple levels. Chromatin remodeling complexes are integral components of genome-wide-acting processes, such as DNA replication, DNA damage repair and chromosome condensation and cohesion. Moreover, these factors are also involved in controlling the expression of cell cycle regulatory factors. The SWI/SNF, CHD, ISWI and INO80 subclasses of SNF2-related chromatin remodeling factors are depicted. The members of these subfamilies that are discussed in this article are listed. Protein complexes are in green, ATPase subunits are in black.

assembly of nucleosomes. In this manner, chromatin remodeling factors affect the composition of a nucleosome and regulate higher-order chromatin structure (9-14). Hence, in spite of the inherent stability that is conferred to the nucleosome through multiple histone-DNA contacts (15), chromatin is a highly dynamic entity that varies in structure throughout the cell cycle.

In this review, we will discuss the role of ATP-dependent chromatin remodeling machines in cell cycle control. We will distinguish between their functions in global processes, such as DNA replication, chromosome cohesion, or DNA repair, and their activity in the specific regulation of cell division cycle genes. We will also integrate current knowledge about the cell cycle dependent regulation of the remodeling factors themselves.

3. MULTI-LEVEL ACTION OF CHROMATIN REMODELING FACTORS IN CELL CYCLE CONTROL

ATP-dependent chromatin remodeling factors are typically organized in multiprotein complexes. Their catalytic subunits belong to the SNF2 family of ATPases that are structurally related to *S. cerevisiae* Swi2/Snf2 protein (16, 17). Based on sequence similarities in their ATPase domains and according to the presence or absence of additional protein motifs outside of the ATPase domain 24 SNF2 subfamilies have been defined (18). The SWI/SNF, ISWI, CHD and INO80 ATPases have been studied most extensively. There are considerable variations in complex composition within each subfamily. For example, in humans, multiple SWI/SNF complexes with partially overlapping subunit composition can co-exist in a cell, and it is not yet clear whether they have distinct or redundant functions (for details about remodeling complex composition see 19, 20). The non-SNF2-family subunits in these complexes have diverse functions that include recruitment to the sites of action, interaction with other proteins and direct modulation of the properties of the ATPase (14, 21, 22).

Over the past decade, research has shed light on the roles of chromatin remodeling factors and their participation in various pathways of cell cycle control. It has become apparent that chromatin remodeling factors operate at different levels to affect cell cycle progression. On one hand, they engage in processes that preserve general chromatin integrity, such as chromosome duplication, sister chromatid cohesion or DNA damage repair. On the other hand, ATP-powered chromatin remodeling complexes act in a gene specific way to control the expression of important cell cycle regulators (Figure 1). As chromatin remodeling complexes do not bind to DNA in a sequence-specific manner, direct and indirect interactions between dedicated complex subunits and sequence-specific recruiting factors are likely responsible for the assignment of a complex to a specific task.

4. GLOBAL CHROMATIN REMODELING

4.1. DNA Replication

Replication of the genome is a complex process that involves multiple steps of chromatin modification including nucleosome mobilization for efficient origin recognition, chromatin decondensation and dissassembly at the replication fork and chromatin re-assembly and establishment of epigenetic marks on the duplicated DNA strands. Nucleosomes can block firing of a replication origin *in vivo* (23), and assembly of DNA into chromatin leads to a general inhibition of replication efficiency *in vitro* (24-26). Thus, reorganization of chromatin structure around replication origins is a prerequisite for pre-replication complex formation. However, relatively little is known about the mechanisms that guide nucleosome remodeling and dissassembly at replication origins and replication forks (27).

Chromatin remodeling complexes of the SWI/SNF and ISWI families have been implicated in regulating replication origin accessibility (Figure 2). Studies in *S. cerevisiae* have shown that the SWI/SNF complex is involved in the activation of a subset of replication origins. The autonomous replicating sequence (ARS) 121 requires the presence of an intact SWI/SNF complex for full activation (28). Also in yeast, a link was observed between the RSC complex and DNA replication. RSC is the closest relative of SWI/SNF. Depletion of its Sfh subunit (the ortholog of mammalian SNF5) along with the cell-cycle regulated Rsc3 subunit resulted in a shift of cell ploidy suggesting an important role for RSC in S-phase regulation (29). *In vitro* studies with the *Drosophila*

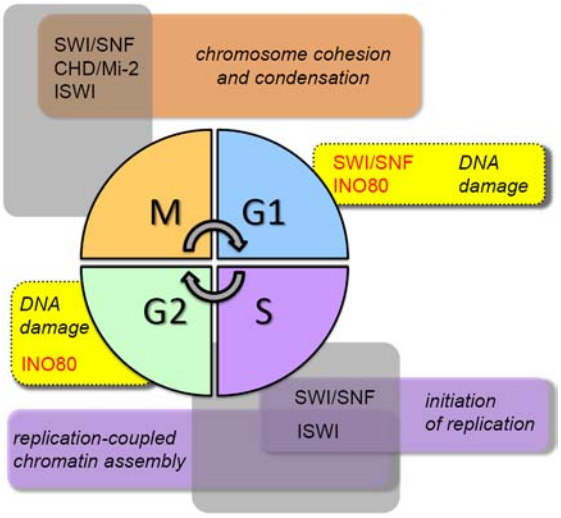

Figure 2. The SWI/SNF, ISWI, CHD and INO80 classes of SNF2-related ATPases participate in processes that act on a genome-wide scale to preserve genome integrity at different stages of the cell cycle.

CHRAC complex, which belongs to the ISWI family of chromatin remodelers, demonstrated that CHRAC was able to remodel the nucleosomal structure at the SV40 replication origin resulting in enhanced replication initiation efficiency (26). Moreover, a recent analysis of the Epstein-Barr-virus (EBV) origin of plasmid replication (OriP) revealed a role for SNF2h (the human ISWI homolog) in the remodeling of positioned nucleosomes at OriP at the G1/S border. SNF2h-mediated remodeling at this origin appeared to facilitate histone deacetylation and MCM3 loading during early S-phase. OriP is usually active in late S-phase. Thus, the combined action of SNF2h and histone deacetylases might determine proper timing of origin firing (30). Notably, late S-phase replication of the inactive rRNA genes in mammals is dependent on the NoRC complex, which also contains the SNF2h ATPase. Overexpression of the NoRC component Tip5 in 3T3 cells led to an increase in the number of rRNA genes that were replicated late in S-phase. This shift in replication timing was accompanied by the transcriptional silencing of these rRNA genes (31). It is possible that selective recruitment of specific ATP-dependent remodelers to particular replication origins affects the timing of origin firing. Specifically, generation of either repressive or "open" chromatin conformations (by alternative action of ISWI or SWI/SNF factors) might translate into either late or early replication initiation.

4.2. Replication-coupled chromatin assembly

Nucleosome assembly requires the concerted action of histone chaperones, which bind and deliver the histones to the sites of assembly, and ATP-dependent remodeling factors, that facilitate histone loading and positioning of the nascent nucleosomes (for reviews see 32, 33). The role of histone chaperones in nucleosome reconstitution has been studied extensively *in vitro* and *in vivo*. Since a detailed overview of these studies is beyond the scope of this article, the reader is referred to a number of excellent reviews on this topic (34-38). Here, we will briefly discuss the contribution of ATP-dependent factors to nucleosome assembly during replication. The ISWI containing complex ACF in *Drosophila* and the human SNF2h ATPase have both been implicated in replication-coupled chromatin assembly (Figure 2; 39-41). Inactivation of ACF in flies led to acceleration of S-phase in syncytial embryos. Similarly, mutant larval neuroblasts exhibited a shortening in heterochromatin replication timing. These findings suggest a particular requirement for ACF for the assembly of repressive chromatin structures (39). In mammalian cells, it was found that SNF2h localizes to heterochromatic replication foci as a component of two distinct remodeling complexes. One complex contained the human ACF1 subunit, and RNAi mediated depletion of ACF1 compromised cell cycle progression (41). The other complex, termed WICH, contained the Williams syndrome transcription factor (WSTF). WSTF can interact with the DNA polymerase processivity factor PCNA and, thereby, might target SNF2h to heterochromatic replication foci (42). Collectively, these studies suggest that ISWI-related remodeling factors are critically involved in the assembly and potentially also in the remodeling of heterochromatic chromatin during replication.

It is of interest to note in this context that impairment of nucleosome assembly by ablation of the above mentioned factors does not trigger cell cycle arrest. This indicates that cells are able to tolerate a certain amount of chromatin structure perturbation. Nevertheless, the sensitivity of cells towards changes in global chromatin architecture might depend on their developmental or differentiation stage. The analysis of the biological role of *Drosophila* CHD1 has revealed that this factor is necessary for the reorganization of paternal pronuclear chromatin during fertilization by incorporating the histone variant H3.3. Loss of CHD1 prevents the paternal pronucleus from entering into mitosis (43). Thus, in this developmental setting, perturbation of global chromatin structure is no longer compatible with normal cell cycle progression. Likewise, the expression of a dominant-negative form of ISWI in *Drosophila* embryos resulted in general decondensation of chromosomes, defective spindle organization and embryonic lethality (44). It was shown in this study that polytene chromosomes isolated from *Iswi* mutant flies exhibited a general reduction of linker histone H1 association, suggesting a role for ISWI in the formation of higher-order chromatin structure. Despite these recent discoveries, there is still much to be learned about the functions of ATP-dependent remodeling factors in the course of chromosome duplication. For instance, no specific remodeling factor has yet been directly linked to the replication-coupled assembly of euchromatic DNA. It remains to be shown whether SWI/SNF complexes are also involved in the remodeling of metazoan origins. Moreover, it is not known, which mechanisms trigger nucleosome disruption ahead of the replication fork (45).

4.3. Chromatin remodeling factors and mitosis

Apart from their role in S-phase, ATP-dependent chromatin remodelers also affect progression through mitosis. Different classes of remodeling factors have been

linked to chromosome condensation, association of cohesins, centromere assembly as well as spindle and centrosome integrity (46; Figure 2). Depletion of various RSC subunits revealed a critical role of RSC during mitosis, although the responsible mechanisms remained elusive (29). Moreover, the RSC complex has been shown to be required for the association of cohesin along the arms but not at the centromere of *S. cerevisiae* chromosomes. The loss of the Rsc2 subunit as well as a temperature-sensitive mutation of the catalytic Sth1 subunit resulted in premature sister chromatid separation, elevated frequency of chromosome loss and accelerated entry of yeast cells into the budding stage (47). A link to cohesin association and/or function was also observed for the human ISWI homolog SNF2h and the Mi-2 containing NuRD complex. These factors were found to co-immunoprecipitate and co-localize with the cohesin complex component Rad21 (48).

Deletion of the CHD family member Hrp1 in *S. pombe* gave rise to multiple chromosome segregation defects. Therefore, Hrp1 was suggested to function in chromosome condensation and/or in the loading of the histone H3 variant CENP-A onto centromeres (49, 50). Surprisingly, a link between centrosome function and ATP-dependent chromatin remodeling factors has been uncovered recently. Sillibourne and colleagues (51) showed that CHD3/Mi-2α and CHD4/Mi-2β associate with pericentrin, which is a major component of the centrosome. Knock-down of CHD3/Mi-2α by RNAi resulted in the dissociation of pericentrin from the centrosome and various mitotic defects. It remains enigmatic, however, how CHD3/4, which are chromatin remodeling factors, might function at the centrosome.

From these studies it is evident that various ATP-dependent remodelers not only affect the structure of the nucleosome but that they are also intimately linked to the higher-order organization of chromosomes. As most of our knowledge about these functions stems from studies in budding yeast, it will be interesting to learn whether similar factors have similar functions in metazoans.

4.4. DNA repair

There are many different types of DNA damage ranging from base damage and mismatches to helix distortion and strand breaks. Consequently, a variety of mechanisms and pathways are at work to repair DNA damage. Their common purpose is to prevent the accumulation of mutations and/or the inhibition of important processes, such as replication and transcription. Over the past few years, great progress has been made towards an understanding of the functions of chromatin remodeling complexes in different DNA damage repair pathways. Direct involvement in DNA repair has been shown for RSC and SWI/SNF, INO80, SWR1 as well as Rad54. These factors were found to have diverse functions in repair, which include nucleosome displacement at DNA double-strand break sites (INO80), histone exchange (SWR1), nucleosome remodeling (SWI/SNF, Rad54) and facilitation of cohesin loading (RSC) at sites of DNA damage (for recent detailed reviews on remodeling factor involvement in DNA damage repair see 52-55).

Besides their direct participation in repair processes, some chromatin remodelers have also been linked to the control of DNA damage checkpoints (Figure 2). In the initial reports on INO80 function in double strand break (DSB) repair in yeast it was observed that checkpoint response was unaffected in an *ino80* mutant (56, 57). A more recent study, however, showed that *ino80* mutants are unable to undergo checkpoint adaptation (58). This phenomenon allows yeast cells that are arrested in G2 following DNA damage to overcome cell cycle arrest despite the presence of unrepairable double strand breaks. The mechanism by which INO80 might contribute to checkpoint adaptation is not known.

A link between RSC activity and DNA damage checkpoint activation was established by the analysis of mutations of the Rsc2 subunit. *Rsc2* mutants exhibited reduced phosphorylation of the histone variant H2AX at DSB sites. Consequently, the Tel1 and Mec1 kinases were not recruited efficiently to the DSB, which resulted in defective activation of the G1 checkpoint kinase Rad53 (59). Mec1/Tel1 kinases, which correspond to the mammalian ATM/ATR kinases, were also found to directly target the INO80 complex. Phosphorylation of the Ies4 subunit of the INO80 complex appears to affect complex activity and resulted in increased checkpoint response (60).

Taken together, chromatin remodeling complexes have emerged as crucial components of different DNA repair pathways. By remodeling nucleosome structure at the sites of DNA damage they facilitate recruitment of the repair machineries as well as enhance the efficiency of the repair process. Moreover, they contribute to the signaling of DNA damage and, thus, to the regulation of cell cycle progression.

5. GENE SPECIFIC FUNCTIONS OF ATP-DEPENDENT CHROMATIN REMODELING FACTORS IN CELL CYCLE REGULATION

5.1. SWI/SNF complexes and E2F target gene regulation

Numerous studies have examined the role of ATP-dependent chromatin remodelers in the transcriptional regulation of important components of the cell cycle machinery. In particular, the mammalian SWI/SNF complexes have become known as key regulators of cell proliferation and differentiation, and several complex subunits have been recognized as tumor suppressor proteins (20, 61-63). SWI/SNF complexes in mammals either contain the ATPase BRM (human brahma) or BRG1 (brahma related gene 1). BRG1 can associate with two partially overlapping sets of proteins to constitute the BAF and PBAF complexes, respectively, while BRM is only found in BAF-like complexes (19, 20, 62). Additional variation is possible within BAF-like complexes through mutually exclusive association of the ARID1A and ARID1B subunits, which are orthologs of the *Drosophila* Osa protein (64).

Mammalian SWI/SNF complexes have been identified as critical co-regulators at many E2F target genes

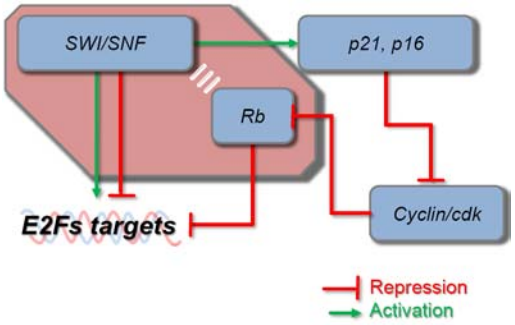

Figure 3. SWI/SNF complexes regulate activation as well as repression of E2F target genes in mammals *via* different pathways. Transcriptional repression can be achieved by direct interaction of SWI/SNF with the negative regulator Rb protein at E2F target gene promoters. Alternatively or in addition, SWI/SNF can activate the expression of cdk inhibitors and thus prevent the inactivation of Rb protein by cyclin D/cdk. For transcriptional activation of E2F target genes, SWI/SNF complexes can directly associate with activating E2F transcription factors to remodel the nucleosomal structure at the target gene.

(65, 66). Although they can positively affect cell proliferation, their activity as negative regulators of proliferation is more obvious. Accordingly, BRG1 deficient mouse embryos die early in development and mice heterozygous for a BRG1 deletion are prone to develop cancer (67). Moreover, reintroduction of BRG1 into SW-13 cells, which do not express BRG1, induces growth arrest and reversal of the transformed phenotype (68). Moran and colleagues (69-71) showed in recent studies that activating and repressive functions, respectively, of SWI/SNF complexes in cell cycle regulation depend on whether the complex contains ARID1A or ARID1B. ARID1A-specific complexes appear to exert their anti-proliferative function by direct repression of critical cell cycle regulator genes, such as cdc2, cyclin E, cyclin A or cyclin B2 (65, 66, 69). Thereby, they associate primarily with the repressor E2Fs, E2F4 and E2F5. Conversely, ARID1B-specific complexes promote cell proliferation by activating cell cycle genes in conjunction with activator E2Fs, such as E2F1 (69).

Several studies suggest that SWI/SNF complexes may act in concert with different factors to regulate E2F target genes. For instance, it was shown that repression of E2F targets correlates with the simultaneous presence at these promoters of SWI/SNF components, the Sin3a co-repressor and the histone deacetylases HDAC1, HDAC2 and HDAC3 (69). Moreover, it was shown that SWI/SNF complexes directly interact with the retinoblastoma (Rb) protein to repress several E2F target genes and to induce cell cycle arrest (68, 72, 73). In addition, cell cycle dependent association of the Rb-SWI/SNF repressor complex with an HDAC was found to coordinate the sequential expression of cyclin E and cyclin A (74). Thus, SWI/SNF complexes can collaborate with E2F transcription factors to activate the respective target genes, yet they also can associate with Rb protein to repress transcription of these genes (Figure 3).

5.2. SWI/SNF and the regulation of $p21^{WAF1}$

SWI/SNF repressor function does not always require interaction with the Rb protein (e.g. 75, 76). Instead, SWI/SNF can regulate the activity of Rb by indirectly affecting its phosphorylation state (Figure 3). It was found that SWI/SNF contributes to the activation of the cdk inhibitor $p21^{WAF1}$ (69, 71, 75). BRG1 overexpression resulted in the upregulation of $p21^{WAF1}$ expression. Elevated levels of $p21^{WAF1}$ prevented phosphorylation of Rb protein by cdk2, thereby maintaining the repression of cell cycle genes. Notably, in this study, cell cycle arrest did not require direct interaction between Rb protein and BRG1 (75). The $p21^{WAF1}$ promoter is also targeted by the p53 cell cycle regulator, and SWI/SNF has been implicated in p53-mediated regulation of $p21^{WAF1}$. Transfection of p53 along with SNF5 (a subunit of SWI/SNF complexes) or BRG-1 into C33A cells caused increased expression of the endogenous $p21^{WAF1}$ gene. Consistently, a physical interaction between p53 and the SWI/SNF components was observed in this system (77). These data link SWI/SNF to the p53 pathway to control cell cycle arrest. However, $p21^{WAF1}$ expression was also induced in the absence of p53 upon overexpression of SNF5 in the breast cancer derived cell line ALAB (78). Not only transcriptional activation but also repression of the $p21^{WAF1}$ gene seems to involve SWI/SNF complexes, albeit in an indirect way *via* upregulation of c-myc. SWI/SNF-mediated activation of c-myc results in the inhibition of $p21^{WAF1}$ expression (69, 71). Thus, depending on the intracellular environment, regulation of $p21^{WAF1}$ expression can be controlled by various regulatory pathways. Yet, most of these diverse mechanisms appear to involve a SWI/SNF complex.

In contrast to the $p21^{WAF1}$ promoter, the c-myc promoter is also a direct target for repression by SWI/SNF. Mouse embryonic fibroblasts that lack BRM exhibit elevated levels of c-myc (79). Conversely, c-myc expression is reduced in human tumor cells that overexpress BRG1 (78). This example illustrates the ability of SWI/SNF complexes to activate as well as to repress transcription of the same gene (e.g. c-myc). One explanation for this phenomenon might be that distinct SWI/SNF complexes with alternative subunit compositions are active at the promoter. However, it remains unknown how different subunits contribute to the SWI/SNF-mediated establishment of alternative chromatin conformations that either result in transcriptional repression or activation.

5.3. Distinct roles of the SNF5 subunit of SWI/SNF complexes in cell cycle regulation

SNF5 is a core subunit of all human SWI/SNF complexes and has a particularly important role in tumor suppression. Mutations of SNF5 are associated with the formation of malignant rhabdoid tumors (MRT), an aggressive type of pediatric cancer (reviewed in 19, 80). Moreover, SNF5 is absolutely required for the survival of normal cells (81). The molecular basis of SNF5-mediated cancer development was examined in a series of studies. For instance, it was shown that SNF5 inactivation in different mouse tissues leads to an upregulation of many E2F target genes (82), and that regulation by SNF5

involves the Rb pathway (83, 84). Moreover, increased p53 levels were observed in SNF5 depleted cells leading to apoptosis, polyploidy and growth arrest (85). The mechanisms responsible for the G1/G0 arrest of MRT derived cells upon reintroduction of SNF5 might involve upregulation of the $p16^{INK4a}$ tumor suppressor protein (86). However, in a different MRT line, $p16^{INK4a}$ upregulation by SNF5 induced cellular senescence but not G1 arrest suggesting that SNF5 uses a $p16^{INK4a}$ -independent way to confer cell cycle arrest (87). $p16^{INK4a}$ is an inhibitor of cyclin D1/CDK4 kinase, which phosphorylates Rb. Hyperphosphorylation of Rb protein leads to dissociation of the protein from E2F transcription factors, resulting in the activation of E2F target genes and cell proliferation (88). Some of the E2F target genes that respond to SNF5 levels have been linked to mitotic defects and aneuploidy. Thus, it was suggested that restoration of normal ploidy in MRT cells upon reintroduction of SNF5 might be caused by re-establishment of the normal regulation of these E2F target genes. Therefore, defective SNF5 not only relieves G1/G0 arrest of the cell cycle but also causes chromosomal instability, both of which are required for cancer development (76).

Despite ample evidence that establishes SNF5 as a tumor suppressor and critical cell cycle regulator, it is not known, if SNF5 functions via SWI/SNF complexes or if it has additional activities. Furthermore, the mechanistic roles of SNF5 in the course of chromatin remodeling and/or promoter targeting of the remodeling complex are poorly understood. It will be a challenging task for the future to elucidate the specific functions of SNF5 in the remodeling of cell cycle genes to regulate their coordinate expression.

5.4. Mechanistic basis of SWI/SNF mediated cell cycle regulation

The molecular mechanisms of SWI/SNF action in these regulatory circuits have not been studied in great detail. Many *in vitro* reports, however, have demonstrated that SWI/SNF complexes remodel chromatin in a way that generally destabilizes chromatin structure (reviewed e.g. in 10, 12, 14, 89). For instance, SWI/SNF can increase the accessibility of restriction enzymes to nucleosomal DNA, catalyze the loss of nucleosomes and mediate the transfer of histones between DNA templates. Consistent with these activities, a recent genome-wide study of nucleosome structure in response to elimination of the RSC subunit Sth1 revealed a gain of nucleosome density at RNA polymerase III genes. Likewise, a locally more restricted gain of single nucleosomes in RNA polymerase II promoters that are RSC targets was observed in these *Sth1* mutants (90).

Only few studies have so far addressed the molecular changes of promoter structure in cell-cycle regulated genes. One example is provided by the cyclin A promoter, which was shown to exhibit increased DNA accessibility upon gene activation (91). Two positioned nucleosomes that are present at the inactive promoter in quiescent mouse embryonic fibroblasts are lost upon entry of the cells into S-phase. This loss correlates with the loss of BRM from the cyclin A promoter. Likewise, increased accessibility of promoter proximal regions was observed in $BRM^{-/-}$ cells, which show constitutive expression of cyclin A (91). Thus, it was concluded that BRM exerts its repressive effect by maintaining the positioning of repressive nucleosomes at the cyclin A promoter. However, it should also be considered that in proliferating cells, BRG1 was found to interact with the cyclin A promoter (66, 69, 79, 92). Thus, an alternative possibility may be that the increased accessibility of promoter sequences upon cyclin A induction is caused by BRG1-mediated chromatin remodeling rather than the loss of BRM-mediated nucleosome positioning. Such a function of BRG1 was observed during STAT3-mediated activation of the $p21^{WAF1}$ gene, when recruitment of BRG1 to the $p21^{WAF1}$ gene promoter resulted in increased micrococcal nuclease accessibility of the promoter region (93). Hence, at the inactive cyclin A promoter, BRM might function to counteract recruitment of BRG1.

Clearly, more work has to be done to illuminate the molecular basis of gene activation and repression by SWI/SNF and to discern the relative contributions of different SWI/SNF complexes. It will be particularly interesting to delineate the molecular mechanisms by which SWI/SNF complexes confer transcriptional repression of target genes. Transcriptional repression is usually linked to the establishment of a more compacted chromatin structure (94-97). Thus, the generally observed activities of SWI/SNF to destabilize nucleosome structure do not easily explain its role in transcription repression.

6. REGULATION OF CHROMATIN REMODELING FACTORS

Compared to the wealth of information that exists about the biochemical and cellular functions of ATP-dependent chromatin remodeling factors, knowledge about their own regulation is limited. Expression of the ATPase encoding genes appears to be fairly constant throughout the cell cycle. Moreover, members of the SWI/SNF, ISWI and CHD classes of remodelers are expressed across a wide range of tissues in multicellular organisms. There are, however, other mechanisms by which the activity of these regulators can be controlled. For instance, both BRM and BRG1 are phosphorylated in a cell cycle dependent manner (98, 99). Phosphorylation occurs during mitosis and results in the inactivation and redistribution into the cytoplasm of human SWI/SNF complexes (99). Dephosphorylation after exit from mitosis was found to restore remodeling activity of SWI/SNF. It is not known which enzymes are responsible for this modification. Although the MAP kinase ERK1 and phosphatase 2A, respectively, were found to phosphorylate/dephosphorylate BRG1 and BRM *in vitro*, *in vivo* evidence for this is still lacking (99). The reasons for phosphorylation-mediated inactivation of SWI/SNF during mitosis are not well understood. It was suggested that SWI/SNF activity needs to be restricted to facilitate general transcriptional inhibition during mitosis (98). On the other hand, however, the SWI/SNF complex was found to be necessary for the transcription of mitotic genes in budding yeast (100). It is possible that also in metazoans, SWI/SNF complexes are required for mitotic transcription by

counteracting local chromatin compaction. In this situation, a subset of SWI/SNF complexes might have to be protected from mitotic phosphorylation to be able to accomplish such a function.

In addition to BRG1 and BRM, several other components of human SWI/SNF complexes can be modified by phosphorylation. For instance, BAF155, BAF60 and SNF5 are targets for phosphorylation by kinases such as ERK1, protein kinase B/Akt, p38 or cyclin E/cdk2 (99, 101-103). The effects of phosphorylation by these enzymes on the remodeling activities of SWI/SNF have not been studied. Yet, it appears that the targeting of the complex to specific promoters might be affected. For example, it was shown that inhibition of p38 resulted in decreased recruitment of SWI/SNF to muscle specific regulatory elements (101).

Phosphorylation was observed to also regulate members of other classes of SNF2-related remodeling factors. The CHD-group enzyme dMi-2, which is a component of the NuRD repressor complex, is phosphorylated by casein kinase 2 (104). Dephosphorylation of dMi-2 resulted in increased nucleosome mobilization and nucleosome-stimulated ATPase activity suggesting that phosphorylation might destabilize the interaction with the nucleosome substrate (104). In contrast to human SWI/SNF, however, phosphorylation of dMi-2 does not seem to be cell cycle dependent. In the case of ATRX, a SNF2-like protein that has been associated with X-linked mental retardation syndrome accompanied by α-thalassemia (ATR-X), phosphorylation also occurs at the onset of mitosis and is hardly detectable during interphase (105). While the significance of this modification on ATRX remains elusive, phosphorylation of the INO80 complex by Mec1/Tel1 kinases has recently been linked to DNA damage checkpoint response (60; and see above).

Acetylation is another modification that has been shown to regulate SWI/SNF activity (106). Acetylation of two lysine residues in the carboxy-terminal domain of BRM negatively affects its transactivation activity. Furthermore, substitution of these residues by arginines, which mimicks the unacetylated state, increased the growth inhibitory potential of BRM, presumably by stabilizing the interaction with Rb protein (106). Site-specific acetylation also occurs on remodelers of the ISWI and CHD classes (107; S. Morettini and A. Lusser, unpublished observation). Acetylation of *Drosophila* ISWI on a lysine residue within the HAND domain of the protein by the acetyltransferase GCN5 does not result in any change in ATPase activity, and it is presently not known whether it affects the remodeling and/or targeting activities of ISWI (107). Sumoylation has been observed on the ATRX-related protein ARIP *in vivo*. The analysis of a sumoylation deficient mutant revealed that ARIP ATPase activity was lost and its function as a transcriptional co-activator of androgen receptor regulated genes was severely compromised (108).

Collectively, these studies suggest important roles of posttranslational modifications in the regulation of ATP-powered remodeling proteins. These regulatory marks appear to affect different aspects of remodeler function, such as direct inhibition or stimulation of catalytic activity, complex composition, complex targeting or even participation in signaling pathways. Considering the multitude of processes in which chromatin remodelers participate, it is conceivable that their activity needs to be carefully regulated. We are currently only at the beginning to understand the mechanisms that control ATP-dependent chromatin remodeling factors and their cross-talk with the cell cycle machinery.

7. PERSPECTIVES

Chromatin structural changes and cell division cycle progression are inseparable processes that constantly and reciprocally affect each other. Thus, the mechanisms and factors that catalyze chromatin modifications are key components of the cell cycle regulatory machinery. Much has been learned in recent years about the role of chromatin modifying proteins in DNA-utilizing processes, such as transcription, DNA replication or damage repair. ATP-powered chromatin remodeling complexes have emerged as co-regulators of cell cycle events acting on a genome-wide scale as well as in a gene specific manner. Yet, many intriguing and challenging questions remain to be solved. For instance, we are only at the early stages of understanding the identity and molecular functions of ATP-dependent factors during the initiation of DNA replication or the removal of histones from parental DNA strands during replication. Even the reassembly of nucleosomes after replication fork passage is only partially understood. It will also be important to delineate the contribution of chromatin remodeling factors to the establishment and disruption of higher-order chromatin folding during the cell cycle.

Further research into the specific roles of SWI/SNF complexes in regulating the transcription of crucial cell cycle regulator genes should illuminate the complex ballet of association/dissociation of different SWI/SNF complexes with target promoters. Furthermore, the contribution of other remodeler classes to the regulation of cell cycle-specific gene expression has not been studied in great detail yet. In a recent report from budding yeast, the involvement of two ISWI-related proteins, Isw1 and Isw2, in transcriptional repression of the cell cycle regulator gene *CLB2*, which controls G2/M and M/G1 transitions, was demonstrated (109). Thus, it is likely, that also in metazoans remodelers other than SWI/SNF are at work to control cell cycle specific gene transcription. In addition, the analysis of the regulation of ATP-dependent chromatin remodeling factors by posttranslational modifications, degradation, intracellular compartmentalization and other mechanisms should aid the understanding of how chromatin remodeling factors are incorporated into cellular signaling pathways. Finally, it will be important to examine the relationship between ATP-dependent factors and other chromatin modifications,

such as covalent modifications of histones and incorporation of histone variants.

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Abbreviations: ACF: ATP-utilizing chromatin assembly and remodeling factor; ARIP: androgen receptor interacting protein; CHD: chromodomain-helicase-DNA binding domain; CLB2: cyclin B2; CHRAC: chromatin accessibility complex; ISWI: imitation switch; NoRC: nucleolar-remodeling complex; NuRD: nucleosome remodeling and deacetylase; RSC: remodels the structure of chromatin; SNF2: sucrose non fermenting 2; Swi2: switch 2; SWR1: Swi2/Snf2 related 1; WICH: WSTF-ISWI chromatin-remodeling complex;

Key Words: Chromatin, Chromatin Remodeling Factors, Cell Cycle, SWI/SNF, Cancer, DNA Replication, DNA Damage, Cdk Inhibitor, Retinoblastoma Protein, Transcription, Review

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