Minireview

Chromatin remodelling and actin organisation

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Abstract Chromatin remodelling is a prerequisite for nuclear processes, and cells have several different ways of remodelling the chromatin structure. The ATP-dependent chromatin remodelling complexes are large multiprotein complexes that use ATP to change DNA–histone contacts. These complexes are classified into 4 sub-families depending on the central ATPase. The switch mating type/sucrose non-fermenting (SWI/SNF) complexes are mainly involved in transcriptional regulation, and this means that they are involved in many processes, such as the formation of actin filaments in the cytoplasm. SWI/SNF complexes are involved in the regulation of genes expressing cell adhesion proteins and extracellular matrix proteins. Actin is also present in the nucleus, affecting transcription, RNA processing and export. In addition, actin and actin-related proteins are subunits of SWI/SNF complexes and the INO80-containing complexes, another subfamily of ATP-dependent chromatin remodelling complexes. Not all functions of the actin and actin-related proteins in the complexes are yet clear: it is known that they play important roles in maintaining the stability of the proteins, possibly by bridging subunits and recruiting the complexes to chromatin.
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Keywords: Chromatin; SWI/SNF; INO80; SRCAP; B-WICH; Nuclear myosin 1; Actin; Actin related proteins; MAL

1. The chromatin structure and chromatin remodelling

The DNA in eukaryotic chromosomes is organised with proteins to form a structure called chromatin. In order for processes that need access to the DNA to proceed, the chromatin structure needs to be altered [for review see [1]]. The major targets in the remodelling process are the nucleosomes, which constitute the smallest unit in the chromatin structure. The nucleosome is built up of a histone protein core around which 146 bp of DNA is wrapped, and alterations in the interactions between DNA and histones, together with the recruitment of nuclear proteins, cause changes in the chromatin structure. These changes in chromatin are the result of two activities: the histone-modifying enzymes, which alter the histone tails post-translationally, and the ATP-dependent chromatin remodelling complexes, which use the energy from ATP to change the DNA–histone contacts and induce sliding or bulking of DNA in nucleosomes [2,3]. Both of these modes of activity are involved in transcriptional activation, transcriptional repression, replication, recombination and DNA repair, and they are involved in the formation of heterochromatin at specific chromosome regions.

1.1. Histone-modifying enzymes and ATP-dependent chromatin remodelling

The histone tails can have several different kinds of post-translational modification: acetylation, methylation, phosphorylation, ubiquitinylation, sumolation, and ribosylation [2]. These modifications occur at specific sites on the histone tails, and several enzymes have the same activity. Acetylation of histone tails is linked to increased accessibility of the DNA and occurs in active genes. The specific histone acetyltransferases (HATs) are recruited to the genes by gene-specific transcription factors and by other histone modifications. The result of methylation is more diverse – it occurs both in active genes and in heterochromatic regions, depending on the site of methylation on the histone tail. Specific histone methyl transferases methylate the different sites on the histones and operate in different regions of the chromosome, recruited by factors or by non-structural RNA [2].

The ATP-dependent chromatin remodelling complexes can be classified into at least four different families depending on the central ATPase: SWI/SNF (or BRG1/BRM associated factor (BAF) complexes) with a SWI2/SNF2 ATPase, ISWI-complexes with an ISWI-ATPase, Mi-2 with a chromodomain-helicase-DNA binding protein (CHD) as ATPase, and the INO80 family [1]. The ATPases are conserved across evolution, as are the binding partners of the complexes and their functions. Several other ATPases that belong to the same family have been found in most species, but these have not been characterised in full. Each cell contains several complexes, and although all of the complexes characterised so far are involved in transcription, they also are involved in other nuclear processes: switch mating type/sucrose non-fermenting (SWI/SNF) complexes are mainly involved in transcription, ISWI-complexes in replication and transcription, Mi-2 complexes in transcriptional repression, and INO80 type complexes in

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Abbreviations: SWI/SNF, switch mating type/sucrose non-fermenting; ISWI, imitation of SWI; CHD, chromodomain-helicase-DNA binding protein; BAF, BRG1/BRM associated factor; RSC, remodels the structure of chromatin; ROCK, Rho kinase; SRF, serum response factor; TCF, ternary complex factor; MAL, megakaryocytic acute leukemia; SWR1, Swi2/Snf2 related; NuA4, nucleosome acetyl-transferase histone 4; SRCAP, SNF2-related CBP-activating protein; TIP60, tat interactive protein 60 kDa; TRRAP, transformation-transactivation domain-associated protein; ARP, actin-related protein; HAT, histone acetyl-transferase; HMT, histone methyl-transferase; HDAC, histone deacetylase; EMT, epithelial–mesenchyme transition

DNA repair. ATP-dependent chromatin remodelling often acts simultaneously on the same genes or regions as those on which post-translational histone-modifying enzymes act [1,2]. Many of the isolated complexes contain actin and actin-related proteins, and these proteins are thought to be true subunits of the complexes [4]. Here, I will discuss two different aspects of the role of actin and actin-related proteins (ARPs) in chromatin: the effect of ATP-dependent chromatin remodelling complexes on actin filament organisation in the cytoplasm, and the role of actin and ARPs in chromatin remodelling complexes during transcription and DNA repair.

1.2. The SWI/SNF complexes

SWI/SNF complexes function as global gene regulators, altering the chromatin structure and changing the accessibility of DNA. Two types of SWI/SNF complex have been isolated from yeast, the RSC (remodels the structure of chromatin) and the SWI/SNF complexes, with two different ATPases, STH1 and SWI2/SNF2, respectively [5]. These complexes consist of 12–15 subunits, which are homologous. The SWI/SNF is involved in transcriptional regulation of a subset of genes [5], whereas the role of the RSC complex is less clear, since it contains proteins coded by essential genes. Mammalian cells have two ATPases: the brahma-related gene (BRG1) and the mammalian brahma (BRM), which are components of two different forms of SWI/SNF complex [5]. The ATPases are 86% similar and many functions are redundant. However, they also exhibit specificity: BRG1 works with zinc-finger proteins whereas BRM works with ankyrin proteins. The other 7–12 subunits are shared, but preferential constellations are present in cells. At least two different constellations have been purified biochemically, the BRG1-specific PBAF and the BAF complexes. Two complexes, BAP and PBAP, have been isolated from *Drosophila*, although only one ATPase exists, Brahma [5].

2. Chromatin remodelling and actin filament organisation

2.1. The effect of SWI/SNF on the actin filament system in mammalian cells

Many tumours and tumour cell lines are deficient in SWI/SNF components, most often the ATPases BRG1 and BRM [6,7]. Reintroducing the missing subunit restores SWI/SNF activity and results in cell cycle arrest, often accompanied by morphological changes, such as flat cell formation [8]. BRG1 extopically expressed in the adrenal adenocarcinoma cell line SW13, which is deficient in both BRG1 and BRM, induces a change in cell morphology, and actin bundles that resemble stress-fibres in fibroblasts form in the cytoplasm [9]. The state of the actin filament system is tightly regulated by several signalling pathways, actin regulatory proteins, and cell adhesion molecules [for review see [10] and Section 1, this issue]. In fibroblasts, growth factors and other signalling molecules induce the formation of stress-fibres, lamellae and filopodia by activating the small GTPases RhoA, Rac and cdc42, respectively (see Section XX in this issue). The activity level of RhoA (RhoA-GTP), however, does not change in BRG1-expressing SW13 cells [9]. Instead, these cells have an increased level of the Rho effector molecule ROCK1, which works down-stream of the RhoA-GTPase. The increased level of ROCK1 protein results in a changed balance between the two RhoA effector proteins ROCK (Rho kinase) and Dia, which both contribute

to the actin filament organisation [11]. BRG1expression also increases the cell surface receptor CD44 in SW13 cells [12], which may further promote the formation of actin filament bundles. Microarray studies of the expression pattern in BRG1-expressing SW13 cells show that the levels of actin-binding protein mRNAs, such as the mRNA for transgelin, are upregulated [13]. However, overexpressing transgelin did not cause actin bundles to be formed in SW13 cells (P. Asp and A-K. Östlund Farrants, unpublished results). The expression levels of 80 genes change on BRG1 expression; many of these genes code for cell surface proteins [13].

The BRG1 protein introduced into another cell line that is deficient in BRG1 and BRM, the breast cancer cell line ALAB, causes cell cycle arrest and the formation of flat cells [14]. Similar changes in the actin filament system to those observed in SW13 cells take place also in ALAB cells upon BRG1 expression (P. Asp and A-K. Östlund Farrants, unpublished results). Microarrays from BRG1-expressing ALAB cells show that the expressions of actin regulatory proteins such as tropomyosin, osteonectin/SPARC, moesin and α-actinin are up-regulated rather quickly, and that the expression levels of many cell adhesion proteins and extracellular matrix interacting proteins are changed [14]. These changes may contribute to the change in cell morphology that occurs on BRG1 expression. In contrast, BRG1 knock-down in a pancreatic tumour cell line, Mia-PaCa2, causes a morphological change to flat cells associated with an increase in actin stress-fibre-like structures [15]. The discrepancy between the effects in SW13 cells and those in Mia-PACa2 cells may be due to differences between the cell types: one difference being that SW13 has a disturbed retinoblastoma (Rb) pathway and mutated p53 [16], while MiaPaCa2 has disruptions in the Rb pathway, p53-pathway and an activated ras pathway [15]. Cross-talk between ras and Rho-signalling pathways does take place [17], and different states of the ras pathway in the SW13 and MiaPAC2a cells create different cell signalling contexts that may affect the response to BRG1 expression.

The effect of BRG1 on cell morphology has also been investigated in fibroblasts stably expressing dominant-negative BRG1 [18]. These cells are larger than the parental fibroblasts, and the morphological changes are accompanied by an increase in paxillin-containing focal adhesion points, whereas the number of stress-fibres remains the same. The levels of other adhesion proteins, such as integrins and urokinase-type plasminogens, are also changed in these fibroblasts; however, these changes do not always take place at the mRNA level. The mechanism may be similar to that in BRG1 expressing SW13 cells. The increase in ROCK seen in BRG1 expressing SW13 cells may be a result of a reduced degradation by the proteasome, since the formation of stress-fibre like actin filament bundles is mimicked by protease inhibitors (P. Asp and A-K Östlund Farrants, unpublished results).

Other SWI/SNF subunits than the SWI/SNF ATPases BRG1 and BRM also affect the cell morphology. When the SWI/SNF core subunit INI1/SNF5, which is directly linked to rhabdoid tumour development [7], is introduced into INI1-deficient MON cells, a change in morphology occurs: the cells become rounder and loose stress-fibres [19]. Similar to the ALAB microarray experiment, changes in expression patterns upon INI1 expression are observed in focal contact proteins, extracellular matrix proteins and cytoskeleton proteins. Paxillin-containing focal adherence also decreases in

these cells to a certain extent [19]. The time for induction of these genes is several days, however, suggesting that these are indirect targets. Signal transduction pathway proteins, such as the cytokine pathway, the Notch pathway and the Wnt pathway, are induced early, and, therefore, more likely candidates for direct target-genes. A further SWI/SNF subunit, BAF57, causes flat cell formation when introduced into BAF57-deficient cells, but no further studies of the actin filament organisation have been conducted [20]. Nevertheless, these studies further emphasise that the whole SWI/SNF complex functions in the regulation of cell architecture. Despite the variety in morphological response to SWI/SNF defects, these results allow us to conclude that SWI/SNF complexes are important for maintaining the proper levels, both directly and indirectly, of signalling molecules, actin regulatory proteins, cell adhesion proteins and proteins that interact with the extracellular matrix. SWI/SNF affects their expression levels, and possibly also their rates of degradation, in cell-specific ways. On the other hand, BRG1 binds to actin directly, in the C-terminal part, and promotes actin filament polymerisation in vitro [21]. Whether this activity is physiologically important for the formation of actin filaments in the cytoplasm remains to be seen. BRG1 and BRM are found exclusively in the nucleus, which makes it unlikely that they are involved in actin filament formation in the cytoplasm. Nevertheless, this activity may have relevance in the nucleus, which will be discussed below.

2.2. The effect of SWI/SNF on actin filament organisation in yeast

The functional conservation between ATP-dependent chromatin remodelling complexes in eukaryotic cells is illustrated by the fact that SWI/SNF complexes in yeast are involved in actin filament organisation. Microarrays of swi2 (deletion of the ATPase) cells showed that SWI/SNF deficiency reduces the expression levels of tropomyosin and of other actin regulatory proteins [22,23]. These cells grow slowly, but their morphology is not severely modified. On the other hand, temperature-sensitive mutants in the other SWI/SNF-type complex, the yeast RSC-complex, cause changes in cell architecture, with defects in the actin filament organisation and sensitivity to microtubule-destabilising agents [24]. No cortical actin cables are formed in RSC-temperature-sensitive mutants at high temperature; instead actin lumps are spread in the cytoplasm, and defects occur in the formation of mating projection. The cause for this defect in actin filament organisation is found in the protein kinase C (PKC) signal transduction pathway and it has been suggested that RSC affects the expressions of genes that code for components of the pathway. Complexes from the SWI/SNF family regulate the actin filament system, although the types of gene that are regulated seem to be different. To this end, it is worthy of note that the PKC pathway is responsible for the binding of SWI/SNF to and remodelling of chromatin following signalling during T-cell activation [25].

2.3. The effect of SWI/SNF on the regulation of actin cytoskeleton genes

The organisation of the actin filament system in cells is highly dynamic, and controlled by environmental stimuli that activate signalling pathways and actin-regulatory proteins. The signalling pathways, mainly Rho-pathways, responsible for regulating the actin cytoskeleton induce the formation of stress-fibres, lamellae and filopodia in the cytoplasm and gene expression in the nucleus [10]. This couples cellular architecture to transcriptional regulation, and evidence has emerged that the link is conferred by actin and actin regulatory proteins, sensing the state of the actin filament system and thereafter regulating the transcription of genes involved in actin dynamics. In the nucleus, the transcription factor SRF (serum response factor) is central in the response and controls the activation of actin cytoskeletal genes on Rho stimulation [reviewed in [26]]. Many signalling transduction pathways converge on SRF; these pathways are activated by the MAP kinase pathway, Rho-GTPases, and cell–cell contacts and regulate early immediate genes, such as c-fos and c-egr1, actin regulatory genes, such as vinculin and tropomyosin, and genes specific to smooth muscle, such as telokin and SM22/transgelin, in response to different signalling pathways. Interestingly, the groups of genes regulated by SRF and SWI/SNF are similar [26], and it is possible that some SRF-regulated genes require SWI/SNF for proper activity. Not all SRF target genes are SWI/SNF-dependent, ruling out the simple explanation that SRF-mediated expression requires SWI/SNF.

The specificity in the genes activated by SRF in response to various signalling pathways is conferred by interactions with different co-regulators: skeletal muscle differentiation genes with the transcription factor MyoD, cardiac differentiation genes by GATA4, with myocardin for genes involved in smooth muscle differentiation, and with TCR for genes in cell growth [26]. In addition, SRF, together with the transcription factor MAL/MRTF-A/MKL1/BSAC protein, regulates actin cytoskeletal genes. The state of the actin filament system is sensed by megakaryocytic acute leukemia (MAL), directly binding monomeric actin. MAL is cytoplasmic at high monomeric actin concentrations and accumulates in the nucleus following stimuli that cause actin filaments to form [27]. Vartianinen et al. [28] have recently shown that the mechanism behind the nuclear accumulation is inhibition of MAL nuclear export at low actin levels, and this results in accumulation of MAL in the nucleus and a subsequent gene activation of actin cytoskeletal genes [27,28]. These results suggest that the cytoplasmic and the nuclear state of actin reflect each other. The accumulation of MAL in the nucleus as such is not sufficient for gene activation, since MAL associated to actin binds SRF at the promoter region without inducing transcription [27,28]. It is probable that MAL-actin instead recruits repressors or inhibits the recruitment of activators. MAL–SRF, with or without associated actin, does not require BRG1 or SWI/SNF for gene activation of cytoskeletal genes. However, a recent study shows that BRG1 interacts directly with MAL, and is required for the activation of smooth muscle genes regulated by MAL–SRF [29]. The authors suggest a model in which BRG1 is required for the binding of SRF to low affinity MAL–SRF binding sites (smooth muscle specific genes), but not for the binding of SRF to promoter regions with high affinity binding sites [29]. This means that SRF specificity depends on the DNA sequence of response elements and the chromatin environment at the different types of gene. This has already been shown for SRF–TCF-dependent genes regulated by the MAP kinase pathway, since these genes are regulated by SRF–ETS response elements [26]. Taken together, mammalian SWI/SNF complexes are not involved in gene activation coupled to changes in the actin filament organisation mediated by SRF, while they are involved in the activation of SRF-controlled genes in the development of muscle cells.

3. Chromatin remodelling in proliferation, differentiation and development

3.1. SWI/SNF complexes in proliferation and differentiation

SWI/SNF complexes that contain BRG1 and BRM are involved in controlling? the expression of genes required for proliferation and differentiation [1,5]. The expression patterns of the two mammalian ATPases BRG1 and BRM suggest that BRG1-containing complexes influence proliferation and BRM complexes differentiation [30,31]. SWI/SNF complexes of both the BRG1 and BRM type are closely connected to cell cycle regulation, and both BRG1 and BRM are suggested to be tumour suppressor genes [6,7,31]. Both ATPases cause cell cycle arrest in BRG1/BRM-deficient cell lines, and this has been linked to a reactivation of the Rb pathway on restoring the SWI/SNF activity [8]. Other subunits are also missing in many tumour cell lines, suggesting that the complete SWI/SNF complex operates in cell cycle control. However, recent studies of heterozygote BRG1 knock-out mice, and comparison of these with SNF5 knock-out mice, show that there are no genetic links between the Rb pathway and BRG1 and SNF5 [32]. Other studies have also shown that the two SWI/SNF subunits exhibit differences in cancer development, such as the effect on genetic stability [32,33], suggesting that SWI/SNF subunits act independently of the SWI/SNF complex or that certain subunits are required at specific genes to allow for the correct contacts between chromatin components and transcription factors.

3.2. SWI/SNF complexes in development

Chromatin remodelling events are a prerequisite for development, and in particular, the SWI/SNF complexes are involved in the expression of tissue-specific genes. SWI/SNF complexes are implicated in the development of early erythrocytes [34], the cardiac tissue [35,36], hepatocytes [30], the neural plate [37], and skin [38]. BRG1 is essential also in an uncharacterised early step in embryogenesis, since BRG1-null embryos die during preimplantation [39]. This is similar to the case for INI1-null embryos, which also die at the preimplantation step [40]. BAF155 is another SWI/SNF core subunit that has been knocked out in mice, and these mice survive the preimplantation stage but die shortly after with neurological defects [41]. BRM-null mice, on the other hand, are viable, healthy but larger than normal [42]. These findings suggest that complete BRG1-containing SWI/SNF complexes are essential in the early steps of embryogenesis. This is also reflected in the temporal expression of BRM, which is reduced in early embryos, but returns in many differentiating cells [30]. The development of early erythrocytes and vascular cells in extra-embryonic tissue are two early processes in embryogenesis that rely exclusively on the presence of BRG1, and this fact could explain the difference in survival between BRG1 and BRM knock-out mice [34]. It is not clear why BRG1 is required for these processes, but one explanation is that the expressions of the β-globin genes depend exclusively on BRG1-containing complexes [43]. The reason for this selectivity is not on the level of ATPase activity, since cells expressing a BRG1 protein mutated at positions close to the ATPase,without affecting the ATPase activity, exhibited a severely reduced chromatin remodelling over the β-globin locus [43]. The locus displayed a low level of histone acetylation and a high level of DNA methylation, suggesting that the important function of BRG1 is to recruit HATs and DNA-methyl transferases, and not in remodelling nucleosomes.

BRG1 is not essential later in development, nor is it essential for cell survival. BRG1-null fibroblasts are viable, as are cells that are deficient in INI1 or BAF155, but they are more prone to be transformed into cancer cells [39–41]. BRG1 and BRM, as well as other subunits (sometimes even various isoforms), vary in their expression patterns, both in time and in a cell-specific manner. These findings suggest that a shift in the composition of SWI/SNF complexes occurs during development, giving complexes with different specificities [44,45]. SWI/SNF complexes with different specificities are found in neural development, where neural-specific isoforms of the subunits BAF53 and BAF45 are recruited to neural genes, most likely by these neural-specific isoforms [44,45]. Similarly, there are three different isoforms of BAF60, two of which are expressed in a tissue-specific manner [36]. Other subunits that change expression pattern during development are BAF155, BAF170 and isoforms of the BAF250, changes that are correlated with decisions between proliferation and differentiation [46]. Furthermore, SWI/SNF complexes that contain BRG1 are involved in the differentiation of adipose cells and muscle cells [47–50]. BRG1 is responsible for the induction of skeletal muscle, where the expressions of muscle-specific genes, such as the early myogenic gene myogenin, and the late myogenic genes desmin and muscle creatin kinase, depend on the chromatin remodelling activity of SWI/SNF complexes [48,49]. In addition, both smooth muscle and cardiac muscle differentiation require BRG1 for the expression of genes specific to smooth muscle [29,50]. BRG1 binds to MAL directly during smooth muscle differentiation, and aids the association of SRF with weak response elements at muscle specific genes [29]. In cardiac myocyte differentiation, LIM-only co-factors, CRP1 and CRP2, function with SRF–GATA4 to induce genes specific to smooth muscle, a process that also requires BRG1 [50]. BRG1 is involved also in determining the morphology of the heart, where it influences the expression of extracellular matrix proteins [34].

One of the major events during embryonic morphogenesis is the epithelial–mesenchyme transition (EMT), in which the actin filament is reorganised, focal adhesions points are formed, and the cells become more motile (reviewed in [51]). Some parts of this programme, and the reverse mesenchyme–epithelial transition, are mimicked in tumour transformation and metastasis [51]. It is tempting to link these developmental steps to the action of SWI/SNF complexes, in particular, since these complexes are involved in cancer development, and they affect the actin filament by the expression of cell adhesion proteins and cell–cell contact proteins. One event that promotes mesenchyme formation is mediated by Ca^{2+} and Rac-GTPase [52]. Loss of epithelial cell–cell contact, via the E-cadherin junction, is followed by induction of SRF–MAL-mediated transcriptional activation of vinculin and the mesenchyme marker α-actin. Despite the fact that the SWI/SNF complexes are required for activation of some MAL–SRF target genes, these complexes have not been implicated in the EMT. Instead, a subunit, MTS3, of the Mi-2-containing NURD complex [53] is required for the transition. BRG1 over-expression in mesenchyme stem cells leads to differentiation and apoptosis [54]. These findings suggest that SWI/SNF complexes, at least at high levels, are incompatible with maintaining mesenchyme cells undifferentiated, a process important in self-renewal of

stem cells. The self-renewal process seems to be carried out by complexes containing the ATPase ISWI [54]. Instead, BRG1 may be involved in differentiation event, for instance in the formation of epithelial–mesenchymal interactions in limb patterning that occur in late steps in ectodermal development, most probably by regulating genes for cell adhesion proteins [38].

4. Chromatin remodelling and actin

Actin is present not only in the cytoplasm: it has also been found in the nucleus, associated with soluble proteins and with nuclear structures (described in Section 10, this issue). Early studies showed that actin in the nucleus is involved in transcription, but concerns were raised that the nuclear pool of actin was a result of cytoplasmic contamination. In recent years, however, an interest in nuclear actin has emerged and actin is now ascribed many functions in the nucleus – in transcription, in RNA processing and in mRNA export [for reviews see [55,56]]. Actin appears to activate transcription by all three RNA polymerases present in eukaryotic cells, and it has, therefore, been suggested that it is an integral part of both initiating and elongating polymerases. It has been suggested that actin interacts with one of the common subunits, RPABC2 or RPABC3, as well as indirectly associates with the CTD of RNA polymerase II for reviews see [55,56]. Actin participates not only in transcription bound to RNA polymerases, it also recruits a HAT, P2D10, during transcriptional elongation when bound directly or indirectly to the growing RNA [57]. It is still not known, however, what form of actin is involved in transcription, and both monomeric G-actin [28] and transient polymeric actin forms are present in the nucleus [58]. The isoform that seems to be predominant in the nucleus is

β-actin, although many studies have not discriminated between isoforms.

4.1. Actin and the ISWI-containing chromatin remodelling complexes

Actin, together with nuclear ARPs, is present in chromatin remodelling complexes from yeast, *Drosophila* and mammalian cells (and most probably plants) (for reviews see [5,59]) (Fig. 1). ARPs are related to actin, sharing the actin fold and, in some cases, also having ATPase activity [59]. Only SWI/SNF complexes and the INO80 family of complexes of the four ATP-dependent chromatin remodelling families characterised have actin and ARPs as subunits that are bound directly. However, one ISWI-containing complex, B-WICH, contains nuclear myosin 1 (NM1), which interacts with actin at the ribosomal genes in the nucleolus [60]. Based on the presence of NM1 and actin along the RNA polymerase I genes, Ye et al. [61] proposed a model where these proteins constitute an actomyosin molecular motor for transcriptional elongation. NM1 associates with chromatin, forming a "track" with which transient, dynamic actin filaments associated with RNA polymerase I interact, resulting in the two motor proteins pulling the polymerase forwards. Ye et al. [61] used cells that expressed mutant forms of NM1, and only the NM1 mutants that were defective in motor activity failed to interact with RNA polymerase I, and subsequently the RNA polymerase I association with chromatin in the coding region was reduced. The role of polymeric actin in transcription was shown by expressing actin mutant in cells inhibited for RNA polymerase I transcription by specific antibodies. Only actin mutants that stabilised polymeric actin restored transcription. Furthermore, actin-depolymerising drugs, such as latrunculin B and cytochalasin D, also inhibit RNA polymerase I transcription, both in vivo
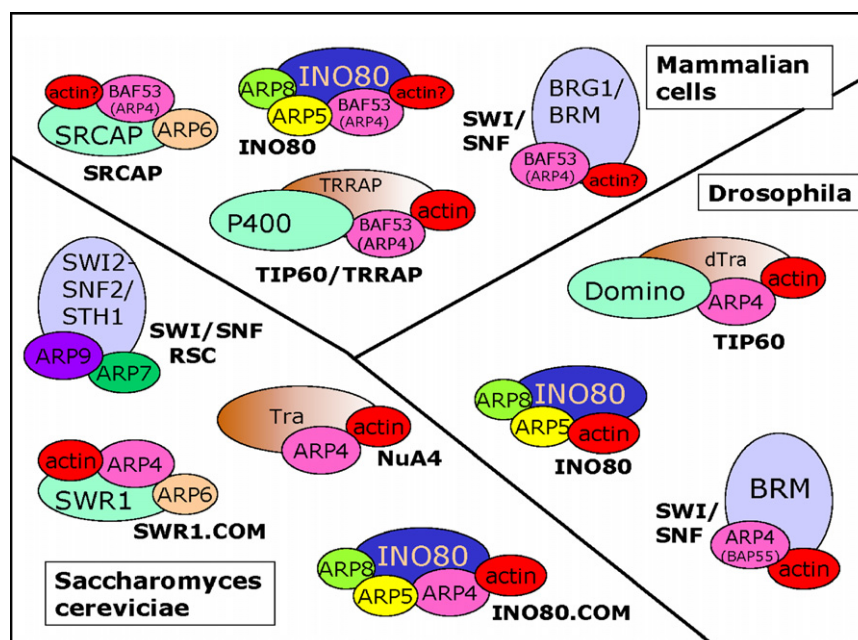

Fig. 1. Comparison of the constellations of chromatin remodelling complexes in mammalian cells, *Drosophila*, and *Saccharomyces cerevisiae*. The complexes for which it is unclear whether actin is a subunit are labelled "actin?". In mammalian cells and *Drosophila*, Tip60/TRRAP have both activities corresponding to the yeast SWR1 and NuA4, and the ATPase is indicated by a turquoise colour (SWR1, SRCAP, p400 or Domino). The ATM-like protein is indicated by Tra/TRRAP. The references to the purifications are given in the text.

and in vitro [61]. A similar mechanism to that described above can be applied to RNA polymerase III transcription, to which B-WICH with NM1 also associates [62]. However, B-WICH is not found at all RNA polymerase III genes, whereas actin is a part of the RNA polymerase III. Actin must be involved in another mechanism on the promoters devoid of NM1. Actin, which changes conformation upon ATP-hydrolysis, may instead operate by functioning as a molecular switch, changing conformation – and therefore interaction partners – between transcriptional initiation and elongation, as well as during elongation discussed in [63].

4.2. Actin in the SWI/SNF family of chromatin remodelling complexes

The yeast SWI/SNF and RSC complexes contain two nuclear ARPs, ARP7 and ARP9, whereas the mammalian and *Drosophila* complexes contain the ARP4 orthologue BAF53 (BAP55), sometimes with actin [1,5]. The ARP7 and Arp9 do not have ATPase activity, but are necessary for stabilising the yeast complexes [5,59]. Similarly, the function of BAF53 in SWI/SNF complexes is to maintain the integrity of the mammalian complexes [5]. The function of actin in the mammalian complexes is to stabilise the ATPase activity of the BRG1, and to bind SWI/SNF to nuclear structures [25]. SWI/SNF complexes are mainly involved in transcriptional regulation by RNA polymerase II, but these complexes also play a role in DNA repair, most likely by a similar mechanism. It is possible that actin in SWI/SNF complexes plays a similar role to the one it plays in RNA polymerase I transcription described above [61]. BRG1 may bind to actin filaments directly in a phosphinositol-dependent manner, similar to the in vitro [21] which may result in short filaments associating SWI/SNF to the RNA polymerases during transcription. It is also possible that actin filaments anchor SWI/SNF complexes to chromatin at RNA polymerase II genes. However, many preparations of SWI/SNF complexes are devoid of actin, whereas BAF53 is present in all SWI/SNF forms. It is difficult to know the reason for this discrepancy in actin association between preparations. In our hands, actin does not co-purify with BRG1 and other SWI/SNF subunits, neither in purifications nor in immunoprecipitations at physiological salt concentrations [J. Ryme, P. Asp, and A-K. Östlund Farrants, unpublished results]. We find actin recruited to some SWI/SNF-dependent promoters [J. Ryme, P. Asp and A-K. Östlund Farrants, unpublished results] and it is possible that actin associates transiently with the SWI/SNF complexes and co-purifies with SWI/SNF complexes under certain conditions. The direct binding of actin to BRG1 [21] could contribute to actin appearing in some SWI/SNF preparations. In addition, ARPs have a preference to bind to actin, and BAF53 could provide another point of interaction with SWI/SNF complexes. Since actin also binds to RNA polymerase II [64], it is possible that actin monomers or polymeric actin forms a bridge between protein complexes that operate in the proximity of one another. Actin could in this way provide a platform between transcription initiation, chromatin remodelling and transcription elongation.

4.3. Actin in INO80 family of chromatin remodelling complexes

The INO80-type complexes have actin and several ARPs bound in a conserved manner. In yeast, two INO80-type complexes have been isolated containing the characteristic split ATPase domains for INO80-type ATPases: the INO80.com contains the ATPase INO80 and the SWR1.com contains the ATPase SWR1 (Swi2/Snf2 related) [1,65]. These complexes are large multiprotein complexes, comprising 8–14 subunits, that share many subunits, among these ARPs and actin. The yeast INO80 complex contains actin and ARP4, ARP5 and ARP8 [59,65] (Fig. 1). The INO80.com plays a role in transcriptional regulation of specific genes (such as genes involved in inositol biosynthesis), in heterochromomatin formation, and in DNA repair. In DNA repair response, INO80.com is recruited to the break site by nucleosomes with a phosphorylated H2A, (H2A-γ). Phosphorylation of the H2A (or the histone variant H2AX in mammalian cells) around the break site by ATM-kinases is an early step in the response to DNA damage. Two of the ARPs, ARP4 and ARP8, in INO80.com have nucleosome-binding activity and may help the subunit Nhp1 to recruit the complex INO80.com to the site of DNA breaks [66,67]. Furthermore, ARP5 and ARP8 function to preserve the integrity of the complex, and deletions of these proteins in yeast cause serious defects in the complex assembly [68]. The INO80.com is required for evicting nucleosomes at the DNA break site at a subsequent step, and this promotes the formation of single strand DNA ends for the repair machinery, and at the same time H2A-γ is removed [66,69]. Another possibility is that the chromatin remodelling activity of INO80.com is used to replace the H2A variant Htz1p (H2A.Z in mammalian cells) with H2A, which can in turn be phosphorylated and keep the damage response active. Htz1p, which is loaded into chromatin during G1 and G2 phases, is found in euchromatin, in particular at inducible promoters and close to telomeres.

The other INO80 family member present in yeast cells, SWR1, is a part of a large, 14-subunit, complex, SWR1.com, which contains actin and ARPs: ARP4 and ARP6 (Fig. 1). The complex has ATP-dependent histone-exchange activity, and loads the H2AZ-H2B into chromatin, thereby preventing heterochromatin regions from spreading along chromosomes [70,72]. Since euchromatin, in particular promoter regions, is densely packed with H2AZ-containing nucleosomes, the SWR1.com has been linked to transcription, but it is also involved in DNA repair. The histone exchange activity of SWR1.com and the HAT-activity of nucleosome acetyl-transferase histone 4 (NuA4) are genetically linked [71], suggesting that a specific acetylation pattern must be present for the H2AZ-H2B to be incorporated into chromatin [65]. This has recently been confirmed, when it was shown that SWR1 requires acetylated histones for its exchange activity [72]. NuA4 is a HAT complex consisting of 13 subunits, and many of these subunits, such as actin and ARP4, are shared with INO80.com and SWR1.com. Similar to the other two complexes, NuA4 is involved in the regulation of transcription, in heterochromatin formation, and in DNA repair pathways [66]. In the repair of DNA double-strand breaks, SWR1.com is recruited later than INO80.com and it has been proposed that SWR1.com exchanges histones, possibly H2A-γ-H2B, for H2AZ-H2B in nucleosomes at the damage site [68]. Another suggestion has been presented by van Attikum et al. [73], who could not observe an accumulation of Htz1p at damaged sites, and thus proposed that SWR1.com is required for correct end-joining and loading of the repair factor Ku80. NuA4 is also recruited to H2A-γ at the site by its ARP4 subunit, and

can thereby open up nucleosomes by its HAT-activity [66]. It has been suggested that NuA4 acetylates H2A-γ, giving SWR1.com the right chromatin environment for exchanging histones in DNA repair or for the loading of proteins that are specific to DNA repair processes [65,67]. In addition to its role of recruiting complexes to nucleosomes, ARP4 promotes the disassembly of the NuA4 complex to form a smaller complex, pico-NuA4, and this changes the HAT-activity from one that is specific for histone 4 to a general histone acetylation activity required for transcription [66].

A similar subunit pattern to that found in yeast is present in complexes purified from mammalian cells and, to some extent, from *Drosophila*: the INO80-containing complex contains orthologues to most of the yeast subunits, including ARP4 (BAF53), ARP5 and ARP8 [74–76] (Fig. 1). Noteworthy, however, is the finding that the ARP4 is not present in the INO80 complex from *Drosophila* [76]. Actin was not present in the first mammalian preparation [74], but it has recently been found in a complex affinity-purified from HeLa cells expressing Flag-hemagglutinin-tagged YY1, a protein that interacts with INO80 [75]. The SWR1 ATPase has two orthologues in human cells, SNF2-related CBP-activating protein (SRCAP) and p400, and one in *Drosophila*, Domino. The two mammalian proteins are found in two separate protein complexes: the SRCAP protein in the SRCAP complex, which resembles the yeast SWR1.com [77], and the p400 in the TIP60/TRRAP complex [78], which is the NuA4 orthologue. The earliest preparation of the SRCAP complex contained BAF53 without actin [77], but actin was recently co-purified with the SRCAP complex in a purification using specific anti-SRCAP antibodies as the last step [79]. However, the authors raised doubts about whether actin and other co-purified proteins, such as different tubulins, are *bona fide* subunits, since these proteins are often found in material analysed by mass spectrometry. The TIP60/TRRAP complex contains both BAF53 and actin [80]. The only SWR1 orthologue in *Drosophila*, Domino (p400), is part of the *Drosophila* HAT TIP60 complex. *Drosophila* TIP60 contains both ARP4 (BAP55) and actin [81]. So far, no orthologue to the mammalian SRCAP has been found in *Drosophila*. The SRCAP-specific ARP6 is present in *Drosophila* cells, found associated to heterochromatin, most likely interacting with heterochromatin protein 1 (HP1) [82]. The function of these complexes in mammalian and *Drosophila* cells is not fully clear. The human INO80 complexes are involved in transcription and DNA repair. INO80 is assembled at homologous end-joining foci and recruited to double strand breaks by YY1 [75]. However, INO80 does not co-localise with foci that have phosphorylated H2AX [75]. The human SRCAP and the *Drosophila* TIP60/TRRAP have histone-exchange activity; in the TIP60/TRRAP complex this activity is combined with the HAT-activity [81]. The human SRCAP loads H2AZ-H2B into chromatin and is involved in transcription, as a co-activator for CREB and nuclear receptors [79]. The *Drosophila* TIP60 exchanges phosphorylated H2Av (which possesses both the ability to be phosphorylated in response to DNA damage and the characteristics of H2AZ of being present in euchromatin) for unmodified H2Av [81]. Both the mammalian and the *Drosophila* TIP60/TRRAP are linked to transcription and DNA repair [71,77,80,83]. In DNA repair, these complexes are recruited to breaks by H2A-γ at the DNA-damage site, and subsequently involved in the removal of the H2A-γ. Two mechanisms have been proposed in human

cells: in the early response, the HAT-activity of TIP60/TRRAP acetylates H2A-γ, which becomes polyubiquinylated and exchanged [81,82]. Later in the response, TIP60/TRRAP acetylates histone 4 in nucleosomes containing H2A-γ, promoting dephosphorylation, most probably by a prior histone exchange mechanism [84]. The acetylation of phospho-H2Av prior to exchange occurs in relation to the action of the *Drosophila* TIP60 complex [81]. The function of actin in these complexes is still unclear, but it may bind ARPs, stabilise complexes and provide binding surfaces for chromatin, other subunits, and interacting factors. Polymeric forms of actin have not been found in chromatin remodelling complexes, and actin is present in stoichiometrical or sub-stoichiometrical amounts (as are the ARPs) [21].

5. Concluding remarks and future perspectives

ATP-dependent chromatin remodelling is an event that influences gene expression at a global level, and other nuclear processes. SWI/SNF complexes affect the cellular architecture, which is determined by the actin filament system, most probably by altering the expression of cell adhesion proteins and signal transduction proteins. It cannot be ruled out, however, that SWI/SNF complexes are also involved in the MAL–SRF regulation of the actin filament dynamics, regulating actin cytoskeletal genes. SWI/SNF is involved in the MAL–SRF induction of smooth muscle during smooth muscle differentiation, in a process in which MAL interacts directly with BRG1. It is still unclear what determines that SWI/SNF complexes are recruited to one type of MAL–SRF. Possible future work is the study of the effect of actin binding to MAL on MAL–SRF complexes at the promoter at the different kinds of MAL–SRF genes. SWI/SNF complexes are also required for GATA-SRF mediated induction of smooth muscle specific genes during cardiac differentiation, together with the bridging factor LIM-only protein CRP2. In addition, actin and ARPs are subunits in chromatin remodelling complexes, and the SWI/SNF subunit BRG1 binds to actin directly in two ways: one of these depends on phosphoinositol, the other does not. The ratio of actin to other subunits does not exceed 1:1, suggesting that monomeric actin is associated with the SWI/SNF complexes or other complexes. However, the association of actin with SWI/SNF complexes is not clear (it is, for example, not found in all purified complexes), and should be investigated further. One possible explanation for the uncertainty of whether actin is present in SWI/SNF complexes is that the binding corresponds to actin dynamics, and thereby reflects the actin status of the cell or the phosphoinositol signalling status. It is generally accepted that actin and ARP are important components in INO80-type complexes and in the HAT NuA4/TIP60, even though actin is not always present in preparations of the mammalian orthologous complexes.

One important issue for future research is the form, monomeric or polymeric, that actin has in the nucleus and in the different nuclear processes. Short, dynamic actin filaments are present in the nucleus, and it has been suggested that these function in transcription recently reviewed in [85]. The stoichiometry in chromatin remodelling complexes suggests that the form is monomeric, most likely bridging different subunits or proteins at the site. The finding that short actin filaments, together with NM1, act as an actomyosin-like driving force in

RNA polymerase I transcription raises questions about the role of actin in other nuclear processes. Do RNA polymerase II and III also use actin-myosin motors during elongation (NM1 is not present on all genes), and what are the roles of the RNA polymerases themselves? Other questions concern the role of actin in chromatin remodelling complexes and whether these complexes can also bind filamentous actin. Can they anchor proteins, such as the RNA polymerases, to chromatin in this way?

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