Diversity and specialization of mammalian SWI/SNF complexes

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The SWI/SNF complex in yeast facilitates the function of transcriptional activators by opposing chromatin-dependent repression of transcription. We demonstrate that in mammals SWI/SNF complexes are present in multiple forms made up of 9–12 proteins that we refer to as BRG1-associated factors (BAFs) ranging from 47 to 250 kD. We have isolated cDNAs for human BAF155, BAF170, and BAF60. BAF155 and BAF170 are encoded by separate genes that are both homologs of yeast SWI13. Both contain a region of similarity to the DNA binding domain of myb, but lack the basic residues known to be necessary for interaction with DNA. The two SWI13 homologs copurify on antibody columns specific for either BAF155 or BAF170, indicating that they are in the same complex. BAF60 is encoded by a novel gene family. An open reading frame from yeast, which is highly homologous, encodes the previously uncharacterized 73-kD subunit of the yeast SWI/SNF complex required for transcriptional activation by the glucocorticoid receptor (Cairns et al., this issue). BAF60a is expressed in all tissues examined, whereas BAF60b and BAF60c are expressed preferentially in muscle and pancreas, respectively. BAF60a is present within the 2000-kD BRG1 complex, whereas BAF60b is in a distinct complex that shares some but not all subunits with the BRG1 complex. The observed similarity between mammalian BAF190, BAF170, BAF155, BAF60, and BAF47 and yeast SNF2/SWI2, SWI3, SWI3, SWP73, and SNF5, respectively, underscores the similarity of the mammalian and yeast complexes. However, the complexes in mammals are more diverse than the SWI/SNF complex in yeast and are likely dedicated to developmentally distinct functions.

[Key Words: SWI, SNF, BRG1, BAF, SWP, chromatin]

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Chromatin is actively remodeled during development, as indicated by the observations that the same genetic locus in different tissues varies dramatically in its sensitivity to DNase I (Weintraub and Groudine 1976; Wu and Gilbert 1981) and restriction enzymes (McGhee et al. 1981). During development of specific cell types, chromatin remodeling of certain genes appears to precede the transcriptional activation of the gene (Siebenlist et al. 1986), suggesting that chromatin remodeling may occur in anticipation of developmental transitions. The mechanisms underlying these developmental changes in chromatin structure are unclear. In Saccharomyces cerevisiae, the products of five genes, SWI1/ADR6, SWI2/SNF2, SWI3, SNF5, and SNF6, are thought to function by remodeling chromatin to aid transcription factors required for specific inducible genes such as HO and SUC2 (Neigeborn and Carlson 1984; Stern et al. 1984; Breeden and Nasmyth 1987; for review, see Winston and Carlson 1992, Carlson and Laurent 1994; Peterson and Tamkun 1995). Recent evidence from both genetic and biochemical studies indicates that these five proteins function together as one multisubunit complex. For example, single and double SWI/SNF mutants were shown to have similar phenotypes (Peterson and Herskowitz 1992). Each of the five SWI/SNF gene products is involved in regulation of the same set of genes (for review, see Peterson and Herskowitz 1992, Winston and Carlson 1992). Immunoprecipitation using antibodies against different SWI/SNF proteins purified all five proteins, indicating they are subunits of one complex. Six additional polypeptides have been found in the complex and two of them were identified as TFG3 and SNF11 (Cairns et al. 1994; Peterson et al. 1994; Treich et al. 1995; Cairns et al. 1996a).

The SWI/SNF complex appears to remodel chromatin structures by an unknown mechanism (for review, see Winston and Carlson 1992; Carlson and Laurent 1994; Wolfe 1993; Peterson and Tamkun 1995). Several genetic suppressors of swi/snf mutants have been identified as components of chromatin, such as H2A, H2B, H3, H4 (Hirschhorn et al. 1992, 1995; Prelich and Winston 1993, Kruger et al. 1995). The chromatin structure at the

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SWI2 promoter is altered in swi/snf mutants, a change that is independent of transcription (Hirschhorn et al. 1992). Moreover, the purified yeast SWI/SNF complex has an ATP-dependent activity that enables it to disrupt mononucleosomes and facilitate binding of GAL4 derivatives to the nucleosome core in vitro (Côté et al. 1994). Thus, one model for the function of the SWI/SNF complex is that it facilitates the ability of transcriptional activators to overcome the repressive effects of chromatin (Travers 1992).

Several lines of evidence suggest that higher eukaryotes contain homologs of the yeast SWI/SNF complex. First, transcriptional activation by the rat glucocorticoid receptor (GR), the Drosophila bicoid factor, and ftz were shown to be dependent on SWI/SNF function when ectopically expressed in yeast (Laurent and Carlson 1992; Peterson and Herskowitz 1992, Yoshinaga et al. 1992). In addition, two Drosophila homologs of the SWI/SNF proteins, brm (a homolog of SWI2) and int (a homolog of SNF5), have been identified and are present in a high-molecular-weight complex similar in size to the yeast complex (Tamkun et al. 1992, Dingwall et al. 1995). brm was originally identified as a suppressor of mutations in polycomb (Kennison and Tamkun 1988), a repressor of several homeotic genes that is thought to act by regionally compacting chromatin (for review, see Moehle and Paro 1994). Thus, brm itself may be involved in modification of chromatin structure. brm and INR1 are required for proper expression of several homeotic genes (Tamkun et al. 1992, Brizuela et al. 1994; Dingwall et al. 1995). Flies lacking either one die at embryonic stages.

In humans, the two closest relatives of SWI2, BRG1 and hbrm, have been implicated to be functional homologs of SWI2 (Khavari et al. 1993; Muchardt and Yaniv 1993; Chiba et al. 1994). Another protein, INI1/ hSNF5, has been reported to be an SNF5 homolog (Kalpana et al. 1994; Muchardt et al. 1995). BRG1 is present in a high-molecular-mass complex of 2 MD, similar in size to the yeast complex (Khavari et al. 1993). Kwon et al. (1994) have reported partial purification of two BRG1-containing complexes from HeLa nuclear extracts by following BRG1 immunoblot reactivity. They showed that their partially purified fractions contain an activity similar to the yeast SWI/SNF complex that can disrupt nucleosomes and facilitate the binding of GAL4 derivatives and TBP to a nucleosome core (Kwon et al. 1994; Imbalzano et al. 1994). We have recently reported complete purification of distinct complexes containing either BRG1 or hbrm using a combination of conventional chromatography and immunoaffinity purification with the BRG1 antibody (Fig. 1; Wang et al. 1996). Two forms of BRG1 complexes, as judged by their different subunit composition, have been purified from this cell line. Complex A, which is the more abundant form in the cell, contains nine subunits with apparent molecular masses of 250, 190, 170, 150, 110, 60, 57, 53, and 47 kD (Fig. 1b, lane 1). The BRF47 subunit of the complex has been identified as INI1/hSNF5 by microsequencing, immunoblotting, and immunopurification (Wang et al. 1996). Purification with an antibody against INI1/hSNF5 yields an almost identical pattern as with the BRG1 antibody (Fig. 1b, lane 2). The data strongly indicate that these nine polypeptides are components of one complex.

Results

Purification of mammalian SWI/SNF complexes

We have purified the SWI/SNF complexes from the human YT cell line using a combination of conventional chromatography and immunoaffinity purification with the BRG1 antibody (Fig. 1; Wang et al. 1996). Two forms of BRG1 complexes, as judged by their different subunit composition, have been purified from this cell line. Complex A, which is the more abundant form in the cell, contains nine subunits with apparent molecular masses of 250, 190, 170, 150, 110, 60, 57, 53, and 47 kD (Fig. 1b, lane 1). The BAF47 subunit of the complex has been identified as INI1/hSNF5 by microsequencing, immunoblotting, and immunopurification (Wang et al. 1996). Purification with an antibody against INI1/hSNF5 yields an almost identical pattern as with the BRG1 antibody (Fig. 1b, lane 2). The data strongly indicate that these nine polypeptides are components of one complex.

Microsequencing and cloning of BAF155 and BAF170 reveals that they belong to the same gene family as yeast SWI3

To define additional subunits of the BRG1 complexes we separated individual subunits of purified complex A by preparative gel electrophoresis and determined the sequence of peptides from BAF155, BAF170, and BAF60 (see Materials and Methods). Four peptide sequences were obtained for human BAF155 after Lys-C endoprote-
mammalian SWI/SNF complexes

Figure 1. Purification of mammalian SWI/SNF complex. (a) Purification scheme for mammalian SWI/SNF complex A. Two different forms of mammalian SWI/SNF complexes (A and B) were present in most cell lines and tissues and both BRG1 and hbrm complexes exist in two forms [Wang et al. 1996]. The purification scheme is for complex A from cultured cells. Purification using animal tissues requires an extra $300 column. (b) The silver stain gel of the purified human SWI/SNF complex A. The antibodies against BRG1 or hSNF5/INI1/BAF47 were used in immunoaffinity purification and were indicated on top of each lane. The eluted polypeptides were named as BAFxx [see text; xx refers the apparent molecular weight]. The band between BAF53 and BAF57 is the immunoglobulin heavy chain.

teinase digestion [Fig. 2]. cDNA clones were isolated from a human Jurkat T cell cDNA library [see Materials and Methods]. Sequencing and mapping of selected clones revealed a single long open reading frame of 1104 amino acids. All peptide sequences obtained from microsequencing were found in this open reading frame. Immunoprecipitation and immunoblotting using an antibody against a region of the clone confirms that it is indeed the gene encoding human BAF155 [see Fig. 8 and below].

Three high-quality peptide sequences were obtained for human BAF170 after Lys-C endoproteinase digestion [Fig. 2a; see Materials and Methods]. Degenerate oligos were designed based on the longest peptide sequence [amino acids 733–752 of the cloned BAF170; Fig. 2a] and were used to isolate cDNA clones from a Jurkat T-cell cDNA library under low-stringency washing conditions. Sequencing of the clones obtained revealed a single open reading frame of 1213 amino acids containing all three peptide sequences from microsequencing. Immunoprecipitation and immunoblotting with an antibody against part of the sequence showed that it is indeed the gene encoding human BAF170 [see Fig. 8 and below].

Interestingly, BAF170 and BAF155 are highly similar to each other; they are 62% identical and 77% similar at the amino acid level [Fig. 3a]. A search of the NR data bank at the NCBI with BAF170 and BAF155 protein sequences using the BLAST program revealed two signifi-
cant matches, yeast SWI3 protein [retrospective probability 10−73] and a second open reading frame from Saccharomyces cerevisiae identified by the genome sequencing project, YFK7 [SwissProtein bank Accession no. P43609, retrospective probability 10−60]. Sequence comparison between SWI3 and YFK7 showed that they are also similar to each other. Overall, they are 30% identical and 52% similar. We will refer to YFK7 as SWI3b [Fig. 3]. The similarity between the two yeast SWI3 genes is much lower than the similarity between the two human genes [Table 1].

The conserved regions of the SWI3 gene family include a myb-like tryptophan repeat and a coiled-coil region

The alignment of the two human and the two yeast genes revealed three conserved regions in all four proteins [Fig. 3a,b]. Region I is the longest and has the greatest similarity of all three regions. Most of the conserved residues are prolines, hydrophobic, and aromatic amino acids, suggesting that this domain is hidden inside of the complex.

Region II of these proteins is a tryptophan-repeat domain, identified originally in the myb family of proteins [Fig. 3c]. This domain is present in two or three tandem repeats in the myb family of proteins from all species and is involved in sequence-specific DNA binding [for review, see Luscher and Eisenman 1990]. Recently, this domain was termed SANT domain and was thought to bind DNA as it does in the myb family of proteins [Aasland 1996]. However, a bacterial fusion protein containing all three conserved regions of BAF170 has no detectable DNA-binding activity, as determined by gel-shift assays [data not shown].

The conserved region III of the SWI3 gene family contains a predicted leucine-zipper region first recognized in the yeast SWI3 gene [Peterson and Herskowitz 1992]. The leucine-zipper or coiled-coil was identified as a dimerization domain for a variety of DNA-binding transcription factors, such as C/EBP, Fos-Jun-GCN4, ATF and Myc-Mad-Max families of proteins [for review, see Johnson and McKnight 1989]. Because the mammalian BRG1 complex contains both BAF155 and BAF170 [see below], it is possible that this coiled-coil region serves as the dimerization domain for the complex.

Table 1. The homology between the human and yeast SWI3 gene homologs

| Identity/similarity | BAF155 | BAF170 | ySWI3 |
|---------------------|--------|--------|-------|
| BAF155              | 62/77% | 62/77% |       |
| ySWI3               | 30/50% | 30/49% |       |
| ySWI3b              | 29/51% | 31/51% | 30/52%|

Each of the two human SWI3 homologs [BAF155 and BAF170] or yeast proteins [SWI3 and SWI3b] were aligned against each other by using the Bestfit program of UWGCG. The calculated percentage of identical or similar amino acids is shown. SWI3b refers to a yeast open reading frame, YFK7 [see text].
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BAF155

1 ................................. AAAAGGCGGTTAGTGTGDDAA 27

BAF170

1 ................................. AAAAGGCGGTTAGTGTGDDAA 27

28 ................................. MVAEGGKEFSGTVQDLRGGD 77

579 ................................. MVAEGGKEFSGTVQDLRGGD 77

77 ................................. MVAEGGKEFSGTVQDLRGGD 77

597 ................................. MVAEGGKEFSGTVQDLRGGD 77

497 ISRVHAFLEQWGLINYOVDAESRPTPMGPPPTSHFHVLADTPSGLVPLOp 546

570 LRSPQVAAQMLNHPERKDVPQPLQLDTYSSRL. ASK. GAS 617

1845 NLPATTTMPSSLPLGPGLGSAAAQSPAIVAAVOGNLLPSASPLPDPGTPL 1194

50 SSLVVQQLQGEOEPVGVSVDSTKLPKLKFLPQGESGLCIAAAK 99

1145 NLPATTTMPSSLPLGPGLGSAAAQSPAIVAAVOGNLLPSASPLPDPGTPL 1194

128 TYNQQSGPDQSLNSHDHMDKTEDVSLQVNCNLTVTLFVPLDID 177

1095 SIIPFGSLADSISINLPAPPNLMGSPPSPVRPGTLPPPNLPVSMANPLHP 1144

902 PKLLGKSIKDI IKRHOGTVTEDKNNASHVVYPVPGNLEEEEWVRPVKKRDK 199

895 QKLVKHWGFYPDSYDTWVHSNDVDAEIEDPPIPEKPWKVHVKWILDTDIFN 277

587 DEEKGKEGDSEKESEKSDGDPIVDPEK . EKEPKEGQEEVLKEVVESEGER 845

597 ATREWTEQETLLLLEALEMYKDDWNKVSEHVGSRTQDECILHFLRLPIED 646

571 ..............................................................

Figure 2. BAF155 and BAF170 are highly similar to each other. The predicted amino acid sequences for human BAF155 (top) and BAF170 (bottom). The underlined sequences indicate the peptide sequences obtained from microsequencing after Lys-C digestion. The proteins used for microsequencing are from human KB cells. The sequences are aligned using the Bestfit program of UWGCG. The sequence of BAF155 was obtained from three overlapping cDNA clones. The total length of DNA is 5188 bp, very close to the size of its mRNA on Northern blot (~5.5 kb). The sequence of BAF170 was obtained from a contiguous cDNA clone of 4022 bp. It is shorter than its mRNA determined by Northern blot (~5 kb; see Fig. 4 for Northern blots).

In addition to these conserved regions, the amino termini of BAF155 and BAF170 are highly similar to each other but not to the yeast genes (Fig. 3a). Their carboxyl termini are highly proline-rich and somewhat glutamine-rich. Pro-rich and Glu-rich domains are common in a variety of transcription activators (Courey et al. 1989; Mermod et al. 1989).

BAF155 and BAF170 are expressed in a wide range of tissues

BAF155 and BAF170 mRNA were found in all tissues that have been examined and were expressed at particularly high levels in muscle (Fig. 4). In addition, Western blots of nuclear extracts from cultured cell lines derived from different tissues show that they are expressed in all cell lines examined (data not shown). Finally, the cDNAs of BAF155 and BAF170 match ESTs obtained from melanoctyes, testis, breast, spleen, liver, placenta, infant brain, and fetal brain for BAF155, and ESTs obtained from liver and spleen, ovary, breast, placenta, fetal brain, and testis for BAF170 (Fig. 4).

BAF60 is a homolog of SWP73, a novel SWI/SNF protein

Six peptides obtained from microsequencing of BAF60 from calf thymus matched to an open reading frame [musd15kl, protein information resource (PIR) accession no. A30222; Fig. 5] adjacent to the mouse glycero1-3-phosphate dehydrogenase gene (Johnston et al. 1989). musd15kl has no known function, but is expressed ubiquitously in mice. To verify that this gene encodes
Figure 3. Human BAF155 and BAF170 belong to the yeast SWI3 gene family. (a) The schematic presentation of conserved regions between two human genes, BAF155 and BAF170 and two yeast genes, SWI3 and SWI3b (SWI3b refers to a open reading frame, YFK7, SW accession no. p43609). The shaded area indicates the conserved regions. The numbers above each shaded box indicate the percentage of identical and similar amino acid residues of each region using the corresponding region of BAF155 as the standard. They were calculated using the Bestfit program of UWGCG. (b) The three highly conserved regions among the SWI3 gene family of proteins. The myb-like tryptophan repeat and predicted coiled-coil region are indicated by a bracket. The asterisks mark the hydrophobic residues in the coiled-coil that are separated by seven amino acids. The alignment was performed using the Pileup and Pretty program of UWGCG. (c) The alignment of the myb-like tryptophan repeat of the SWI3 gene family with myb and other transcription factors (see text). We found that the domain is also present as a single repeat in the nuclear receptor corepressor (N-CoR, Horlein et al. 1995) and transcription factor TFC5 (a subunit of TFIIIB; Kassavetis et al. 1995). The helix-turn-helix structure was based on the solution structure of c-myb DNA binding domain (Ogata et al. 1992). The asterisks indicate the conserved tryptophans. The arrows indicate the amino acid residues that presumably interact with DNA if the domain functions similarly as the domain in c-myb. The computer search of the NR data bank at the NCBI was done using the BLAST search program.
Figure 4. BAF155 and BAF170 are expressed in a wide range of tissues. [a] Northern blot analysis of mRNA from different human tissues as indicated on the top of each lane. The arrows indicate the presence of the mRNA for either BAF155, BAF170, or β-actin. [b] The muscle actin that was also detected by the β-actin probe. BAF155 and BAF170 cDNAs match many EST sequences in the dBEST data bank at NCBI. These EST sequences are derived from several different tissues at different developmental stages, suggesting BAF155 and BAF170 were expressed in these tissues. For BAF155, these tissues include: fetal brain (T06718, R95776), infant brain (z43024), testis (T19008, t25695), breast (R50245, t25696, H21971, R55216), placenta (R67673, R24632), melanocyte (N44961, N36960), liver and spleen (R95825, H54140, H53515, R95825). For BAF170, the tissues include: fetal brain (M61970), ovary (T50228), testis (T19008), breast (R73206, H24688, R73142), placenta (R24526, R24632), spleen and liver (T64879, T91030, T50242).

Cloning of a family of human genes that are related to mBAF60a and SWP73

Based on the sequence of mBAF60a we isolated a family of human genes very similar to mBAF60a by screening cDNA libraries [see Materials and Methods]. We referred to its members as human BAF60a, b, and c. The human BAF60a gene is likely the gene corresponding to mBAF60a in humans, because it has the highest homology to the mouse mBAF60a gene at both the DNA [92% identical] and protein level [98% identical and 99% similar]. hBAF60a is likely a splicing variant because it lacks a region of the mouse gene mBAF60a (amino acids 384–423, Fig. 5) that is present in all other homologs. hBAF60b and hBAF60c are highly similar to BAF60a and to each other (~70% identical and ~80% similar among all three human genes, Table 2; Fig. 5). hBAF60b encodes a predicted protein of 475 amino acids. Immunoblotting with an antibody against hBAF60b showed that it is not detectable in the complex purified with the BRG1 antibody [data not shown]. Its immunoreactivity was found to fractionate as a 500-kD complex on a Superose 6 sizing column, in contrast to BAF60a, which cofractionates with BRG1 as a complex of ~2 MD [Fig. 6; Fig. 9, below]. The sequence of hBAF60c predicts a protein of 469 amino acids. BAF60c is highly expressed in muscle cells [Fig. 7, top], in contrast to BAF60b which is expressed in many tissues with the highest level in pancreas [Fig. 7, middle]. BAF60a was reported to be ubiquitously expressed [Johnston et al. 1989; Fig. 7, bottom].

All three human genes are roughly equal in similarity to yeast SWP73 and SWP73b [Table 2]. The alignment of the three human genes with the BAF60/SWP73 genes from other species showed that they have a divergent amino terminus, but most of the carboxy-terminal part of the protein is conserved. The data strongly suggest that BAF60 and SWP73 belong to a large gene family whose products could be involved in nucleosome remodeling. Searching of the PIR data bank or using the University of Wisconsin Genetics Computer Group (UWGCG) program to analyze the BAF60/SWP73 gene family did not reveal any obvious structures or motifs. However, we noticed that the amino-terminal nonconserved region of BAF60a contains a proline-glycine rich region that is similar to a region in BRG1 and the brm family of proteins.

The hbrm complex has a subunit composition similar to the BRG1 complex

We have shown previously that the two mammalian SWI2 homologs, BRG1 and hbrm, are present in separate complexes [Wang et al. 1996]. As demonstrated above, the BRG1 complex purified with BRG1 antibody contains BAF170, BAF155, and BAF60a. All three subunits are homologs of yeast SWI/SNF proteins. Western blots using antibodies against these proteins confirmed their presence in the BRG1 complex [Fig. 8a]. The complex purified with hbrm antibody contains INI1/hSNF5 as determined by Western blot, and has a pattern of polypeptides on a silver-stained gel similar to that of the BRG1 complex [Wang et al. 1996, see Fig. 8b, cf. lanes l,2]. We immunoblotted the hbrm-associated polypeptides with antibodies against BAF170, BAF155, and BAF60a and found that all three are present in the hbrm complex [Fig. 8c, lane 1]. Thus, hbrm and BRG1 complexes have similar subunit compositions, suggesting that they have similar functions in vivo.
The mammalian SWI/SNF complex contains two SWI3-like subunits

We have shown above that both BAF170 and BAF155 are homologs of the yeast SWI3 gene. Silver stain gels of the complex (Fig. 1b, lanes 1,2; also see Fig. 8b, lanes 1,2) suggest that these two subunits are present in equal molecular ratio in the complex [staining with Coomassie Blue or Ponseau S shows similar results; data not shown]. To determine whether BAF170 and BAF155 are in the same complex or separate complexes, we purified BAF170- or BAF155-associated polypeptides using immobilized antibody against BAF170 or BAF155 and visualized the purified proteins by silver-staining of the SDS-PAGE (Fig. 8b, lanes 3,4) and by Western blotting of the eluted polypeptides (Fig. 8c, lanes 2,3). The data demonstrate that the mammalian SWI/SNF complexes containing BAF170 also contain BAF155 and that those containing BAF155 also contain BAF170.

The diversity of mammalian SWI/SNF complexes as evidenced by the presence of a distinct BAF60b complex

Based on the different tissue distributions of the members of the BAF60 gene family, we explored the possibility that they may define biochemically distinct complexes. Using an antibody against the nonconserved amino terminus of BAF60b, W. affinity-purified the BAF60b-associated polypeptides [see Materials and Methods]. The silver-staining pattern of these polypeptides looks remarkably similar to that of the BRG1 complex purified with the BRG1 antibody (Fig. 9a, lanes 2,3), suggesting that they could be similar or identical. Western blotting revealed that the BAF60b complex does not contain any BAF60a immunoreactivity, indicating that BAF60b and BAF60a are indeed subunits of distinct complexes (Fig. 9b). Conversely, the BAF60b complex contains abundant immunoreactivity for BAF170, BAF155, and BAF47, suggesting that these polypeptides are shared between these complexes (Fig. 9c). In addition, the BAF60b complex contains a subunit [referred to as BAF190x; Fig. 9a, lane 3] that has a similar but slightly slower mobility than the BRG1 subunit. Western blotting showed that it has very low BRG1 immunoreactivity and somewhat higher hbrm reactivity (Fig. 9d). Because several subunits of the mammalian SWI/SNF complex are encoded by gene families, microsequencing will be needed to determine the identities of these BAF60b-associated polypeptides. Preliminary data indicate that in addition to BAF60b, at least one other subunit is different from the BRG1 complex (W. Wang and G.R. Crabtree, unpubl.).

We noted that the molecular mass of all subunits of the BAF60b complex is ~1 MD, which is bigger than the size determined using a Superose 6 sizing column [500 kD]. It is possible that the complex was partially dissociated during the fractionation or that the complex exists in a nonglobular shape. We also noted that the Drosophila NURF complex [Tsukiyama et al. 1995] fractionates at a size similar to the BAF60b complex and contains a subunit of 55 kD. We therefore investigated whether BAF60b is a subunit of the human NURF complex. Using an antibody against the human homolog of ISWI, hSNF2L [Okabe et al. 1992; the antibody is a generous gift of Robert Roeder, Rockefeller University, New York], we found that BAF60b and hSNF2L do not have identical chromatographic properties on a Superose 6 sizing column (Fig. 6) or ion-exchange columns [P11 and DE52; data not shown]. The complex purified with BAF60b antibody does not contain immunoreactivity for hSNF2L (Fig. 9d).

Discussion

Structural and functional similarities between the mammalian and yeast SWI/SNF complexes

We previously described the complete purification of mammalian SWI/SNF complexes and demonstrated that the complexes are heterogeneous and that they contain homologs of yeast SWI2/SNF2 (BRG1 or hbrm) and SNF5 (INI1/hSNF5). The complexes containing BRG1 have nucleosome-disruption activities similar to those of the yeast SWI/SNF complex [Wang et al. 1996]. In this report we demonstrate that BAF170, BAF155, and BAF60 are homologs of yeast SWI3 and SWP73 [see also Cairns et al., this issue]. These results and our earlier work establish the close relationship between mammalian and yeast SWI/SNF complexes and strongly support a conserved and universal function for the SWI/SNF complex in all eukaryotes.

Mammalian SWI/SNF complexes contain two different SWI3 homologs

BAF155 and BAF170 are different homologs of the yeast SWI3 protein. These two subunits are highly similar to each other (62% identical and 77% similar) and both are found in the same complex, because purification of the complex with antibody to one subunit contains the other (Fig. 8). The two proteins also appear to be in equimolar ratio based on visualization by silver staining or Coomassie-blue staining. The presence of a leucine zipper in both BAF155 and BAF170 suggests that these subunits could be contributing to a dimer-like structure by forming heterodimers.

The prediction that the complex has a dimer-like structure can be further supported by molecular weight considerations. The molecular masses of either yeast or mammalian SWI/SNF complex have been determined at 2 MD by Superose 6 sizing columns [Khavari et al. 1993; Peterson et al. 1994]. The total molecular weight of all subunits of either the yeast complex [Cairns et al. 1994; Côté et al. 1994] or the mammalian complex is ~1 MD, half the size determined by sizing columns. One explanation for this apparent paradox is that some or all subunits of the complex are present in two copies. Our finding that the mammalian SWI/SNF complex contains two different homologs of SWI3 provides the strong evidence for such a model.
Identification of a myb-like tryptophan repeat domain in the SWI3 family of proteins

We identified a myb-like tryptophan-repeat domain in all SWI3 proteins (Fig. 3c). This domain was identified originally as tandem repeats in the myb family of proteins (for review, see Luscher and Eisenman 1989) and was recently termed the SANT domain and proposed to be a DNA binding domain [Aasland 1996]. The domain is also present in components of two other known chromatin-remodeling complexes, the ADA2/ADA3/GCN5 histone acetyltransferase complex (Horiuchi et al. 1995; Brownell et al. 1996; Candau and Berger 1996) and the NURF complex [Tsukiyama et al. 1995; Tsukiyama and...
presence of these proteins is indicated by arrows. However, we have not been able to demonstrate any DNA binding activity using a recombinant protein containing all three conserved regions of BAF170 (data not shown). Careful inspection of amino acid residues that should contact DNA based on the solution structure of c-myb (Ogata et al. 1992) revealed that three out of five residues in the SWI3 SANT domain are hydrophobic where these residues are charged or hydrophilic in c-myb [Fig. 3c]. Furthermore, the DNA-protein cross-linking studies showed that the subunits in yeast SWI/SNF complex that contact DNA are not SWI3 [Quinn et al. 1996]. Thus, the SANT domain in the SWI3 family of proteins may play a role other than DNA-binding.

BAF60 belongs to a large gene family that includes a novel yeast SWI/SNF subunit, SWP73

We cloned three closely related human BAF60 homologs: hBAF60a, b and c. These human genes have two yeast homologs [Fig. 5]. Cairns et al. (this issue) demonstrate that one of the two yeast homologs encodes a previously uncharacterized SWI/SNF subunit, SWP73. Null mutations in SWP73 have a phenotype that is similar to other SWI/SNF deletions. Furthermore, yeast lacking SWP73 are unable to activate transcription in response to glucocorticoids in yeast strains containing an introduced glucocorticoid receptor gene and a glucocorticoid responsive promoter. Thus, the work in both mammals and yeast indicates that BAF60a/SWP73 is an integral subunit of the SWI/SNF complex.

Mammalian SWI/SNF complexes and pol II holoenzyme

Recently, the yeast SWI/SNF complex was reported to copurify with SRB proteins and was suggested to be an integral part of the yeast pol II holoenzyme [Wilson et al. 1996]. This result is different from previous reports from two other groups using different purification schemes for the SWI/SNF complex [Cairns et al. 1994, Côté et al. 1994]. In those purifications, the SWI/SNF complex does not contain other components. To date we have isolated cDNA clones for seven out of nine subunits of mammalian SWI/SNF complexes and none is similar to the subunits of yeast pol II holoenzyme [W. Wang and G.R. Crabtree, unpubl.]. The preparation of mammalian pol II holoenzyme has been described recently [Ossipow et al. 1995; Chao et al. 1996]. Its pattern on silver-stained gels [Chao et al. 1996] appears to be distinct from that of the purified mammalian SWI/SNF complex. Thus, when us-

**Figure 5.** Sequence alignment of the BAF60/SWP73 gene family. The sequence alignments of BAF60/SWP73 proteins from mammals, C. elegans, and Saccharomyces cerevisiae. The underlined sequences represent those that are either identical or similar to the peptide sequences obtained from microsequencing. The protein used for microsequencing is from calf thymus, and is therefore possibly identical to the reported sequences from mouse or human. One peptide sequence is of high quality: RELVPE (1). The remaining peptide sequences obtained from microsequencing. The protein used for microsequencing is from calf thymus, and is therefore possibly identical to the reported sequences from mouse or human. One peptide sequence is of high quality: RELVPE (1). The remaining peptide sequences obtained from microsequencing (lowercase). Peptide 3 is more similar to BAF60a, whereas peptide 4 and 6 are more similar to BAF60b. The remaining peptides do not distinguish between different BAFs. Thus, it appears that BAF60b is present in a large amount in BRG1 complex of calf thymus. The sequence mBAF60a refers to musdl5kzl [Johnston et al. 1989]. The published mouse sequence is 3101 bp, which is similar to the size of the mRNA (2.5 kb) as determined by Northern blot. It has no starting methionine and also contains a sequencing error that results in its carbonyl terminus being out of frame. Our human BAF60a clone is 2841 bp (mRNA ~4kb) but it contains an extra 150 bp at the 5’ end. A stop codon was found in frame of the predicted starting methionine. However, the methionine at codon 14 could be the starting codon because it has a better Kozak sequence (3/5 vs. 0/5). The human BAF60b cDNA clone is 1946 bp, smaller than its mRNA (~3 kb). A stop codon was found upstream in frame to the predicted starting methionine. There is also a methionine in between, but it is present in a GC-rich region and in a context of a poor Kozak sequence. The predicted starting codon make the BAF60b protein similar in size to BAF60a and BAF60c. The BAF60c cDNA clone is 1724 bp (the mRNA is ~2 kb). A stop codon was found upstream in frame with the predicted methionine. cBAF60 refers to an open reading frame identified by the C. elegans genome sequencing project, CEZKJ1128. ySWP73 refers to an open reading frame from Saccharomyces cerevisiae, SCPCPETIT. This sequence was shown to encode the SWP73 subunit of the yeast SWI/SNF complex [Cairns et al., this issue]. ySWP73b refers to the yeast sequence YCU2. These sequences were aligned using the Pileup and Pretty programs of UWGCG.

**Figure 6.** BAF60b fractionates as a separate complex on Superose 6 sizing column. Western blotting analysis after fractionation of nuclear extract of human YT cells [DE52/0.3M fraction] by a Superose 6 sizing column [Pharmacia]. Antibodies against BRG1, BAF60a, BAF60b, and hSNF2L were used. The presence of these proteins is indicated by arrows.

Mammalian SWI/SNF complexes

- **Figure 6.** BAF60b fractionates as a separate complex on Superose 6 sizing column. Western blotting analysis after fractionation of nuclear extract of human YT cells [DE52/0.3M fraction] by a Superose 6 sizing column [Pharmacia]. Antibodies against BRG1, BAF60a, BAF60b, and hSNF2L were used. The presence of these proteins is indicated by arrows.
Table 2. The homology between mammalian BAF60 and yeast SWP73 gene families

| Identity/similarity | mBAF60a | hBAF60a | hBAF60b | hBAF60c | cBAF60 | yswp73 |
|---------------------|---------|---------|---------|---------|--------|--------|
| mBAF60a             | 98/99%  |         |         |         |        |        |
| hBAF60a             | 66/79%  | 66/78%  |         | 69/82%  |        |        |
| hBAF60b             |         | 71/82%  | 66/78%  | 52/72%  | 55/74% |        |
| hBAF60c             | 55/73%  | 56/73%  |         | 27/50%  | 27/50% | 25/49% |
| cBAF60              | 28/51%  | 27/51%  | 27/50%  | 26/49%  | 23/45% | 23/47% |
| yswp73b             |         |         |         |         | 23/47% |        |

Each of the mammalian BAF60 homologs or yeast SWP73 homologs were aligned against each other using the Bestfit program of UWGCG. The calculated percentage of identical or similar amino acids are shown as % identical/% similar. mBAF60a refers to a known gene, musdl 5kzl. cBAF60 refers to a C. elegans open reading frame CEZK1128_5. ySWP73 refers to a yeast open reading frame SCPCEPETIT. ySWP73b refers to a yeast open reading frame YCU2 [see text for data-bank access numbers].
by their antibodies. Another possibility is that complexes containing homodimers of either BAF170 or BAF155 are present in cells and are purified preferentially by the corresponding antibodies. Our previous findings that 8WI/SNF complexes purified from some cell lines contain substoichiometric amounts of BAF170 support this view (Wang et al. 1996). A third possibility is that some BAF170 and BAF155 are associated loosely with mammalian SWI/SNF complexes, and they dissociate during purification. (c) Western blot analysis of complexes purified with different antibody columns as shown on the top of each lane. The arrows indicate the immunoreactivity of each BAF. We have frequently observed that the BAF47/hSNF5 antibody recognizes two bands. We suspect that the protein might be phosphorylated.

TCA precipitation. The proteins were separated by preparative SDS-PAGE (7.5%). The gel was then cut into two halves. The gel containing lower-molecular-weight proteins (smaller than the 66-kD marker) was transferred to PVDF membrane and visualized by Ponceau S-staining. The band containing BAF60 was excised and digested with trypsin (Boehringer-Mannheim, sequencing grade) overnight. The other half of the gel containing higher-molecular-weight proteins (larger than the 97 kD marker) was negatively stained with ZnCl2 and developed in imidazole (Zhou and Admon 1995). The bands containing BAF170 and BAF155 were excised and digested with Lys-C endoproteinase (WAKO). The peptides eluted from the PVDF membrane or the gel slice were separated by reverse-phase HPLC and sequenced by automatic amino acid sequencer.

Cloning of the BAF155 subunit

BAF155 was purified using human KB cells as the source. The sequence of four peptides obtained after Lys-C digestion did not match any known genes in the NR databank at NCBI searched with the BLAST program. Luckily, one long peptide sequence (corresponding to amino acids 924–944, Fig. 2) was found to contain the predicted sequence based on the four middle amino acids. A 23-nucleotide oligo was then synthesized based on the sequence from microsequencing.

Cloning of BAF170

BAF170 was purified from human KB cells, and three high-quality peptide sequences were obtained after Lys-C endoproteinase digestion (Fig. 2a). These sequences do not match any known genes or EST sequences in the data bank. Two degenerate oligos were synthesized based on the longest peptide sequence (amino acids 728–748 of the cloned BAF170, Fig. 2a). The oligo sequences are: 5'-AA(G/A)GCIGA(C/T)CCIGCITT(C/T)GG-3' and 5'-GTIGTICCIGCIATICC-3'. They were used for internal PCR reactions using human cDNA from Jurkat T-cells as the template. Over 200 positive clones have been identified. They were analyzed by restriction digestion and PCR mapping and classified into different groups. The representative clones from each group were sequenced, and three overlapping clones were found to encode a single open reading frame containing all peptide sequences from microsequencing.
Figure 9. The diversity of mammalian SWI/SNF complexes as evidenced by the presence of a distinct BAF60b complex. (a) Silver-staining gel of the affinity-purified complex using either BRG1 antibody (lane 2) or BAF60b antibody (lane 3) from human YT cells. The polypeptides that have similar mobilities in both complexes are marked. Since no microsequencing has been done for the BAF60b-associated polypeptides, their identities cannot be conclusively determined by simple use of Western blotting data. They were referred to as BAFx. However, the presence of strong immunoreactivity of BAF155, BAF170 and BAF47/hSNF5 suggest that these polypeptides are also subunits of the BAF60b complex. The BAF110 band is missing in this preparation of the BRG1 complex. We find that BAF110 can sometimes be washed away when using a BRG1 antibody column, but it is always present when using BAF47/hSNF5 antibody column. (b-d) Western blot analysis of the load, flowthrough (FT), and elute fractions of the BAF60b affinity column, respectively, as indicated on the top of each lane. The presence of the immunoreactivity was marked with an arrow. (*) The cross-linked IgG coming off the affinity column that was recognized by the secondary antibody. We noticed that the immunoreactivities of BAF60a, BAF155, BAF170, and BAF47/hSNF5 are all detectable in the flowthrough fraction of the BAF60b antibody column, whereas the reactivities for BRG1 and hbrm were not detected. The data imply that these subunits could be components of complexes other than BRG1 and hbrm. We found that the BRG1 and hbrm complexes are very “sticky” and can be precipitated nonspecifically by several unrelated antibodies. The complexes could then be washed off under high-stringency washing conditions. This could be the reason why BRG1 and hbrm complexes were depleted in the BAF60b antibody flowthrough fractions and were also present at low levels in the elute fractions.

Cloning the BAF60 family of proteins

The BAF60 subunit was purified from calf thymus. The peptides obtained were either identical or similar to a published sequence. The longest clone was sequenced and found to contain a cDNA of 4022 bp. A single open reading frame of 1213 amino acids was identified that contained all three peptide sequences obtained by microsequencing.

Preparation of antibodies and immunoaffinity purifications

Rabbit polyclonal antibodies against BRG1, hbrm and hSNF5/INI1/BAF47 have been described previously [Wang et al. 1996]. The antibodies used in this work are all rabbit polyclonal antibodies. The immunogens are fusion proteins containing either glutathione S-transferase (GST) or the maltose binding protein (MBP); for BAF60b, amino acids 26-93 (fused to MBP). The antibodies were all affinity-purified using the corresponding immunogen as affinity ligands (Harlow and Lane 1988). All except BAF60a antibodies work on immunoprecipitation. They were cross-linked to Protein-A Sepharose (Pharmacia) with DMP (Harlow and Lane 1988) and were used for affinity purification of complexes [Wang et al. 1996].

The human homologs of BAF60, the mouse sequence was used to search the human EST sequence data bank at TIGR and dBEST (NCBI). Five EST sequences were found with high scores.

Cloning the BAF60 family of proteins

The human EST data bank at the National Center for Biotechnology Information (NCBI). Five EST sequences were found with high scores.

**Human EST**

| EST | Data bank | Probability | Gene |
|-----|------------|-------------|------|
| TIGR | 10-70      | BAF60a      |
| TIGR | 10-87      | BAF60b      |
| EMBL | 10-50      | BAF60c      |
| TIGR | 10-124     | BAF60c      |
| TIGR/dbest | 10-18 | Unknown |

Oligonucleotides were designed based on the first three EST sequences for PCR amplification of each sequence. The oligos for each sequence are: EST64722 (nucleotides 2-20 and 224-207), THC48547 (nucleotides 7-24 and 316-299), and F05831 (nucleotides 28-46 and 234-217). The cDNA from Jurkat cells was used as a template for PCR reaction. The amplified PCR products were used as probes to obtain cDNAs as described above (see cloning of BAF155).

Northern blot

The human multitissue blot was from Clontech and was probed with a 4.4 kb fragment of cDNA for hBAF155 and a 2.6 kb fragment of hBAF170 cDNA. The full-length cDNAs for hBAF60a, b and c were used as probes. The β-actin probe was provided by the manufacturer. The probes were labeled by 32P-dCTP using Klenow and random hexamers as primers [1-2 million cpm/ml]. After hybridization, the blot was washed at high-stringency conditions (0.1x SSC, 0.1% SDS, 2x10 min at 55°C) and exposed to Kodak X-ray films for 1-3 days. The same blot was washed and reprobed multiple times using different probes as described above.

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