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Nuclear receptors and chromatin remodeling machinery

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Abstract

Eukaryotic genetic information is stored within the association of DNA and histone proteins resulting in a dynamic polymer called chromatin. The fundamental structural unit of chromatin is the nucleosome which consists of ~146 bp of DNA wrapped around an octamer of histones containing two copies each of four core histones, H2A, H2B, H3 and H4. It is this DNA/protein fiber that transcription factors and other agents of chromatin metabolism must access and regulate. We have developed model systems to study the mechanisms by which steroid receptors control physiological activities by regulating gene expression within a higher order chromatin organization. Our studies have focused on the glucocorticoid receptor and its ability to remodel chromatin which is mediated by the BRG1 complex. Using novel cell systems, we demonstrate that GR-mediated transactivation from chromatin templates requires BRG1 remodeling activity and that other ATP-dependent remodeling proteins cannot substitute for this activity.

Keywords

GR; Chromatin; Epigenetics; SWI/SNF; BRG1; Transcriptional activation

1. Introduction

The temporal and spatial extraction of information from the genome is critical for normal growth and development. Eukaryotes have evolved to encapsulate this genetic and epigenetic information into a highly specialized organelle, the nucleus (Wolffe and Hansen, 2001). Using a combination of histones and non-histone proteins the genome is assembled into a multilayered chromatin architecture that can be spatially divided into the “active” or “inducible” genome-euchromatin, and the mostly “silent” or “inactive” genome-heterochromatin (Horn and Peterson, 2006). However, even within euchromatin the assembly of eukaryotic DNA into chromatin tends to have a repressive effect on gene transcription by inhibiting access of the transcriptional machinery and gene-specific activators to recognition sequences within target promoters (Felsenfeld and Groudine, 2003; Kinyamu and Archer, 2004).

Structural changes in chromatin that accompany transcriptional activation often require multi-protein complexes that manipulate the nucleosomal architecture. Two distinct classes of chromatin modifying enzymes have been identified, one disrupts chromatin structure using ATP-dependent chromatin remodeling, and another whose actions are mediated through covalent modification of histone proteins. The function of histone-modifying enzymes that catalyze post-translational modifications on histones by altering acetylation,

methylation, phosphorylation, and/or ubiquitination patterns have been extensively reviewed and will not be discussed further (Berger, 2002; Neely and Workman, 2002; Wade, 2001; Zhang, 2003). Rather this review will focus on ATP-dependent chromatin remodeling complexes which use the energy derived from ATP hydrolysis to disrupt histone–DNA interactions in the context of steroid hormone activated transcription, highlighting recent studies with the glucocorticoid receptor.

2. ATP-dependent chromatin remodeling complexes

The ATP-dependent chromatin remodeling complexes are able to alter the position and/or stability of nucleosomes in a non-covalent manner to regulate cellular processes including transcription, replication, DNA repair and recombination. These chromatin modifying complexes contain a core catalytic subunit that belongs to the SNF2 super family of ATPases. Generally, these ATP-dependent remodeling machines are divided into four major classes according to the identity of their ATPase subunit: which include SWI/SNF, ISWI, Mi-2/NuRD, and INO80 (Eberharther and Becker, 2004). The SWI/SNF family of chromatin remodeling complexes, which is highly divergent and can exist in multiple forms, has been the best characterized with regard to structure, function, and enzymatic activity. Human SWI/SNF is a large multiprotein complex that contains either BRG1 or hBrm as the central catalytic ATPase, as well as, 10–12 BRG1-associated factors (BAFs), most of which are orthologous to those found in yeast SWI/SNF and RSC (Nie et al., 2000; Xue et al., 2000; Wang et al., 1996b). Interestingly, various SWI/SNF subunits have been found associated with histone-modifying enzymes such as HDAC1/2, protein arginine methyltransferases 5, coactivator-associated arginine methyltransferase 1 (CARM1), within the NUMAC complex (Nucleosomal Methylation Activation Complex), as well as transcription corepressor mSin3A, and tumor suppressor BRCA1 (Sif, 2004). In addition, SWI/SNF subunits have also been shown to interact with DNA replication factors such as CAF-1 and TOPO II within the Williams syndrome transcription factor (WSTF) complex, including WINAC (WSTF-Including Nucleosome Assembly Complex) (Kitagawa et al., 2003) (Fig. 1A). Human SWI/SNF is composed of a heterogeneous mixture of subunits with most purified complexes containing accessory subunits BAF170, BAF155, BAF60, BAF57, BAF53, and BAF47 (Wang et al., 1996a). Although BRG1, alone, is sufficient to stimulate nucleosome remodeling, addition of the core BAF subunits, BAF170, BAF155, and BAF47 have been shown to reconstitute chromatin remodeling to near optimal levels (Phelan et al., 1999). Human SWI/SNF can be further grouped into two subfamilies: BAF (hSWI/SNF-A) and PBAF (hSWI/SNF-B) (Nie et al., 2000; Yan et al., 2005; Lemon et al., 2001). Members of these two groups share similar subunit compositions, but are distinguished by the presence of specific subunits: BAF250 has been found exclusively in the BAF complex whereas BAF200 and BAF180 are exclusively present in PBAF (Yan et al., 2005) (Fig. 1A).

3. Nuclear receptors

The nuclear receptors (NRs) are a large diverse group of eukaryotic transcription factors which play critical roles in a variety of biological processes including development, reproduction, homeostasis, and metabolism, exerting biological effects through their ability to control transcription of target genes upon binding of signaling ligand (Aoyagi et al., 2005). Members of the NR super family have generally been divided into three major categories, type I, II and III receptors. Type I receptors encompass the classic steroid hormone receptors and include the glucocorticoid receptor (GR), estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and the mineralocorticoid receptor (MR). Upon hormone binding, these receptors associate with hormone responsive elements (HREs) within promoter consensus sequences as homodimers, and activate transcription. Type II receptors which include retinoic acid receptors (RAR), thyroid hormone receptor

(TR), the peroxisome proliferator-activator receptor (PPAR), and Vitamin D3 receptor (VDR), and the type III “orphan receptors” that include ER-related receptors, steroidogenic factor factor-1 (SF-1), the nerve growth factor-induced receptor (NGFI-B), the X-linked orphan receptor-1 (DAX-1), and testis receptors (TR2 and R4) are outside the scope of this review and will not be further discussed. These three classes of NRs constitute one of the largest groups of transcription factors which play diverse roles in many cellular and physiological processes by altering target-gene expression. Structurally, all members of the NR super family share a highly conserved organization containing specific functional domains. These domains consist of an N-terminal activation function, AF-1, domain (A/B), a DNA-binding domain, a hinge region, and a carboxy-terminal ligand-binding domain which overlaps a second activation function, AF-2 (Aoyagi et al., 2005).

4. Role of SWI/SNF in NR-mediated transcription regulation

A role for ATP-dependent chromatin remodeling complexes in transcriptional regulation by steroid receptors was initially reported for GR in yeast studies (Muchardt and Yaniv, 1993; Yoshinaga et al., 1992; Fryer and Archer, 1998). To date, numerous reports suggest that ATP-dependent chromatin remodeling complexes influence ligand-induced transcriptional regulation through NRs (Acevedo and Kraus, 2004; Kinyamu and Archer, 2004). The steroid hormone-responsive mouse mammary tumor virus (MMTV) promoter is an established model system to study the molecular details involved in NR-mediated chromatin remodeling and transcriptional activation by SWI/SNF (Fryer and Archer, 1998). When stably integrated into chromatin, the MMTV promoter acquires a highly organized structure where the long terminal repeat (LTR) is organized into a phased array of six nucleosomes (A–F). The region encompassed by nucleosome B harbor HREs for GR and binding sites for other transcription factors including nuclear factor-1 (NF-1), octamer transcription factor (OTF), and TATA binding protein (TBP) (Archer et al., 1992). The transcription factor binding sites found within this region allow for strong promoter activation by glucocorticoids where ligand-bound GR mediates transcription through mechanisms involving chromatin remodeling (Kinyamu and Archer, 2004) (Fig. 2).

The SWI/SNF chromatin remodeling complex has been implicated in transcriptional regulation by steroid receptors based on the reported interactions of GR and ER with SWI/SNF subunits (Fryer and Archer, 1998; Ichinose et al., 1997). Compelling experimental evidence has been reported that supports this view, implicating the BRG1 complex in GR-mediated chromatin remodeling at the MMTV promoter (Trotter and Archer, 2004). The BRG1/hBrm null SW-13 cell line has been used to study GR-mediated chromatin remodeling of the MMTV promoter by the BRG1 complex. Studies in this cell model system established the requirement for BRG1 in GR-mediated chromatin remodeling and the transcriptional activation of a stably integrated MMTV promoter. Although present in SW-13 cells, remodeling activities of ISWI or Mi-2 based complexes are unable to substitute for GR-dependent BRG1 actions such as transcriptional activation, induced transcription factor binding, and chromatin remodeling of the chromatin template. These data established that the reconstituted BAF remodeling complex, in SW-13 cells, can mediate GR-dependent transcription from MMTV and a select number of endogenous promoters such as 11- β -HSB type 2 and p21 (Trotter and Archer, 2004).

The targeting of SWI/SNF to specific gene promoters is thought to take place through the binding of transcription factors, coactivators, or members of the general transcriptional machinery. Interestingly, BAF subunits with bromodomains are known to target acetylated histone tails; likewise, different SWI/SNF components, including BRG1, BAF250, BAF60a, and BAF57, have been reported to mediate critical interactions between NRs and remodeling complexes (Belandia et al., 2002; Inoue et al., 2002; Garcia-Pedrero et al.,

2006). Within the context of NR-mediated transcriptional activation, multiple interactions are thought to be involved in recruitment and stabilization of the SWI/SNF remodeling complex at target promoters and this targeting may be mediated through direct or indirect interactions involving one or more BAF subunits. The interaction between GR and BRG1 appears to be mediated through BAF250 and/or BAF60a of SWI/SNF. Glucocorticoid receptor binding of BAF60a takes place in a ligand independent manner, but is required for efficient GR-mediated transcriptional initiation and remodeling of the MMTV promoter in vivo (Hsiao et al., 2003). By contrast, the interaction between GR and BAF250 seems to be dependent on the presence of ligand (Nie et al., 2000). Although, BAF250 has been shown to be involved in GR-mediated transcriptional activity on unorganized chromatin, this subunit may be dispensable for GR-mediated chromatin remodeling at the MMTV promoter given that the remodeling process is equally as efficient in the human breast cancer cell line, T47D, which expresses BAF180 instead of BAF250 (Inoue et al., 2002; Fryer et al., 2000). Interestingly, data from the SW-13 cell line, which expresses BAF250 but not BAF180, suggest the BAF180 subunit is not required for GR-mediated remodeling at chromatin MMTV because the remodeling process is supported upon reintroduction of BRG1 (Trotter and Archer, 2004). Given the existence of two distinct human SWI/SNF complexes, BAF and PBAF, these results suggest that GR may not discriminate between the two SWI/SNF based complexes and can use either to perform its function.

Two of the best-characterized classes of ATP-dependent chromatin remodeling complexes, the SWI/SNF and ISWI family, show conserved homology from yeast to humans. Biochemical studies suggest SWI/SNF- and ISWI-based complexes have distinct but overlapping chromatin remodeling activities (Narlikar et al., 2001). BRG1 and SNF2h represent the motor protein of these major mammalian remodeling complexes and genetic analysis has indicated that these ATPase activities do not complement each other (Elfring et al., 1994). Both proteins are found complexed with other subunits which appear to be involved in targeting the remodeling activity to gene-specific promoters as well as to enhance the overall ATPase function (Corona et al., 1999; Eberharter et al., 2001; Hassan et al., 2002). To dissect the distinct remodeling function of BRG1 and to determine if ATPase activity from another remodeling protein could function within the context of the SWI/SNF complex, a chimeric protein was created using the ATPase domain of SNF2h flanked by the N- and C-terminal regions derived from BRG1, designated B-S-B (Fig. 2). In vitro remodeling assays suggest the B-S-B chimera is active; however, the mechanism of remodeling appears to be specific and determined by the molecular characteristics provided by the ATPase present (Fan et al., 2003, 2005). In vivo chromatin remodeling assays, using the MMTV reporter system, revealed that the B-S-B chimera was unable to substitute for wild-type BRG1 in GR-mediated transcriptional activity or hormone induced chromatin remodeling assays suggesting the ATPase activities of BRG1 and SNF2h are not functionally interchangeable. These results suggest that BRG1 remodeling activity is absolutely required for hormone-dependent transcription from the MMTV promoter and that this activity cannot be supplied by chimeric proteins containing SNF2h ATPase activity or other chromatin remodeling complexes present (Fan et al., 2005; Trotter and Archer, 2004) (Fig. 2). Although the ATPase domain appears to dictate the outcome of the remodeling event, these studies demonstrate the activities of BRG1 and SNF2h are not necessarily interchangeable regarding NR-mediated chromatin remodeling and transcriptional activation suggesting the different remodeling functions may be critical to their specific biological roles (Fan et al., 2005).

The MMTV promoter can also be used to evaluate transcriptional activation of other NRs. For PR and AR, SWI/SNF remodeling activity is a requirement for hormone-mediated transcriptional activation from MMTV. Studies have shown PR competes with GR for available BRG1 in the presence of glucocorticoid resulting in inhibition of the GR/BRG1

association (Fryer and Archer, 1998). Androgen receptor-mediated transcriptional activation of MMTV is impaired in the absence of BRG1 or hBrm suggesting AR recruitment of SWI/SNF is vital for promoter regulation (Huang et al., 2003). Many studies have utilized the MMTV promoter system to examine the role of the SWI/SNF remodeling complex in NR-mediated transcription regulation and these observations may also be found for other NR-responsive genes. Estrogen receptor (ER) has been shown to require BRG1 activity for ER-mediated transcriptional activity (Chiba et al., 1994; Muchardt and Yaniv, 1993). In BRG1-null cells, ER α -mediated transcriptional initiation of estrogen-responsive genes was diminished; however, upon BRG1 reintroduction, ER transcription activity was found to be restored. Recruitment of the SWI/SNF complex is not limited to the type I NRs. The remodeling complex has also been found to associate with transcription activation of RAR/RXR and VDR/RXR indicating involvement of SWI/SNF in a wide range of NR-mediated events (Hsiao et al., 2003; Koszewski et al., 2003).

5. Concluding remarks

Multicellular organisms use NR-mediated transcriptional mechanisms in response to physiological, metabolic, or environmental signals with the recruitment of functionally distinct and diverse cofactors which appear to be tissue-, receptor-, ligand-, and/or promoter-specific. These cofactors are often found in association with larger protein complexes which await recruitment by activated NRs to site-specific targets. Although, the role of chromatin remodeling in NR-mediated gene activation has been the main focus of this review, the recruitment of other chromatin modifying enzymes including histone acetyltransferases and histone deacetylases, as part of coactivator and co-repressors, also influences transcriptional events. There is evidence that cells utilize ATP-dependent chromatin remodeling complexes to aid in the recruitment of histone modifying enzymes (Peterson and Workman, 2000; Hassan et al., 2001). Although, remodeling complexes, such as mammalian SWI/SNF, have been shown to play important roles in transcriptional regulation mediated by a variety of NRs, these enzymatic complexes have also been associated with transcriptional repression as demonstrated by activated NCoR and Mi-2/NURD complexes (Fujita et al., 2003). Historically, analysis of NR transcriptional activity has focused on the contributions of chromatin remodeling and assembly of the pre-initiation complex; however, clear roles for remodeling complexes in processes, such as elongation, termination, splicing as well as heterochromatin assembly, suggest a potentially larger field of study must be considered (Horn and Peterson, 2006; Sims et al., 2004; Corey et al., 2003; Batsche et al., 2006; Alen et al., 2002; Morillon et al., 2003). Finally, numerous microarray and chip-on-chip data sets clearly point to various classes of hormonally responsive genes that will be dependent on promoter specificity and biological content for a final transcriptional disposition (Wang et al., 2004; Johnson et al., 2006; Wan and Nordeen, 2003). To this end, the clear mechanistic insights gained from functional interactions between ATP-dependent chromatin remodeling machines and nuclear receptors may provide a way forward to better understand the precise sequence of events involved in transcriptional activation.

References

- Acevedo ML, Kraus WL. Transcriptional activation by nuclear receptors. *Essays Biochem.* 2004; 40:73–88. [PubMed: 15242340]
- Alen C, Kent NA, Jones HS, O'Sullivan J, Aranda A, Proudfoot NJ. A role for chromatin remodeling in transcriptional termination by RNA polymerase II. *Mol Cell.* 2002; 10:1441–1452. [PubMed: 12504018]
- Aoyagi S, Trotter KW, Archer TK. ATP-dependent chromatin remodeling complexes and their role in nuclear receptor-dependent transcription in vivo. *Vitam. Horm.* 2005; 70:281–307. [PubMed: 15727808]

- Archer TK, Lefebvre P, Wolford RG, Hager GL. Transcription factor loading on the MMTV promoter: a bimodal mechanism for promoter activation. *Science*. 1992; 255:1573–1576. [PubMed: 1347958]
- Batsche E, Yaniv M, Muchardt C. The human SWI/SNF subunit Brm is a regulator of alternative splicing. *Nat. Struct. Mol. Biol.* 2006; 13:22–29. [PubMed: 16341228]
- Belandia B, Orford RL, Hurst HC, Parker MG. Targeting of SWI/SNF chromatin remodelling complexes to estrogen-responsive genes. *EMBO J.* 2002; 21:4094–4103. [PubMed: 12145209]
- Berger SL. Histone modifications in transcriptional regulation. *Curr. Opin. Genet. Dev.* 2002; 12:142–148. [PubMed: 11893486]
- Chiba H, Muramatsu M, Nomoto A, Kato H. Two human homologues of *Saccharomyces cerevisiae* SWI2/SNF2 and *Drosophila* brahma are transcriptional coactivators cooperating with the estrogen receptor and the retinoic acid receptor. *Nucleic Acids Res.* 1994; 22:1815–1820. [PubMed: 8208605]
- Corey LL, Weirich CS, Benjamin IJ, Kingston RE. Localized recruitment of a chromatin-remodeling activity by an activator in vivo drives transcriptional elongation. *Genes Dev.* 2003; 17:1392–1401. [PubMed: 12782657]
- Corona DF, Langst G, Clapier CR, Bonte EJ, Ferrari S, Tamkun JW, Becker PB. ISWI is an ATP-dependent nucleosome remodeling factor. *Mol Cell.* 1999; 3:239–245. [PubMed: 10078206]
- Eberharter A, Becker PB. ATP-dependent nucleosome remodelling: factors and functions. *J. Cell. Sci.* 2004; 117:3707–3711. [PubMed: 15286171]
- Eberharter A, Ferrari S, Langst G, Straub T, Imhof A, Varga-Weisz P, Wilm M, Becker PB. Acf1, the largest subunit of CHRAC, regulates ISWI-induced nucleosome remodelling. *EMBO J.* 2001; 20:3781–3788. [PubMed: 11447119]
- Elfrink LK, Dearing R, McCallum CM, Peterson CL, Tamkun JW. Identification and characterization of *Drosophila* relatives of the yeast transcriptional activator SNF2/SWI2. *Mol. Cell Biol.* 1994; 14:2225–2234. [PubMed: 7908117]
- Fan HY, He X, Kingston RE, Narlikar GJ. Distinct strategies to make nucleosomal DNA accessible. *Mol. Cell.* 2003; 11:1311–1322. [PubMed: 12769854]
- Fan HY, Trotter KW, Archer TK, Kingston RE. Swapping function of two chromatin remodeling complexes. *Mol. Cell.* 2005; 17:805–815. [PubMed: 15780937]
- Felsenfeld G, Groudine M. Controlling the double helix. *Nature*. 2003; 421:448–453. [PubMed: 12540921]
- Fryer CJ, Archer TK. Chromatin remodelling by the glucocorticoid receptor requires the BRG1 complex. *Nature*. 1998; 393:88–91. [PubMed: 9590696]
- Fryer CJ, Kinyamu HK, Rogatsky I, Garabedian MJ, Archer TK. Selective activation of the glucocorticoid receptor by steroid antagonists in human breast cancer and osteosarcoma cells. *J. Biol. Chem.* 2000; 275:17771–17777. [PubMed: 10748103]
- Fujita N, Jaye DL, Kajita M, Geigerman C, Moreno CS, Wade PA. MTA3, a Mi-2/NuRD complex subunit, regulates an invasive growth pathway in breast cancer. *Cell*. 2003; 113:207–219. [PubMed: 12705869]
- Garcia-Pedrero JM, Kiskinis E, Parker MG, Belandia B. The SWI/SNF chromatin remodeling subunit BAF57 is a critical regulator of estrogen receptor function in breast cancer cells. *J. Biol. Chem.* 2006
- Hassan AH, Neely KE, Vignali M, Reese JC, Workman JL. Promoter targeting of chromatin-modifying complexes. *Front Biosci.* 2001; 6:D1054–D1064. [PubMed: 11532604]
- Hassan AH, Prochasson P, Neely KE, Galasinski SC, Chandy M, Carrozza MJ, Workman JL. Function and selectivity of bromodomains in anchoring chromatin-modifying complexes to promoter nucleosomes. *Cell*. 2002; 111:369–379. [PubMed: 12419247]
- Horn PJ, Peterson CL. Heterochromatin assembly: a new twist on an old model. *Chromosome Res.* 2006; 14:83–94. [PubMed: 16506098]
- Hsiao PW, Fryer CJ, Trotter KW, Wang W, Archer TK. BAF60a mediates critical interactions between nuclear receptors and the BRG1 chromatin-remodeling complex for transactivation. *Mol. Cell Biol.* 2003; 23:6210–6220. [PubMed: 12917342]

- Huang ZQ, Li J, Sachs LM, Cole PA, Wong J. A role for cofactor-cofactor and cofactor-histone interactions in targeting p300, SWI/SNF and Mediator for transcription. *EMBO J.* 2003; 22:2146–2155. [PubMed: 12727881]
- Ichinose H, Garnier JM, Chambon P, Losson R. Ligand-dependent interaction between the estrogen receptor and the human homologues of SWI2/SNF2. *Gene.* 1997; 188:95–100. [PubMed: 9099865]
- Inoue H, Furukawa T, Giannakopoulos S, Zhou S, King DS, Tanese N. Largest subunits of the human SWI/SNF chromatin-remodeling complex promote transcriptional activation by steroid hormone receptors. *J. Biol. Chem.* 2002; 277:41674–41685. [PubMed: 12200431]
- Johnson WE, Li W, Meyer CA, Gottardo R, Carroll JS, Brown M, Liu XS. Model-based analysis of tiling-arrays for ChIP-chip. *Proc. Natl. Acad. Sci. U.S.A.* 2006
- Kinyamu HK, Archer TK. Modifying chromatin to permit steroid hormone receptor-dependent transcription. *Biochim. Biophys. Acta.* 2004; 1677:30–45. [PubMed: 15020043]
- Kitagawa H, Fujiki R, Yoshimura K, Mezaki Y, Uematsu Y, Matsui D, Ogawa S, Unno K, Okubo M, Tokita A, Nakagawa T, Ito T, Ishimi Y, Nagasawa H, Matsumoto T, Yanagisawa J, Kato S. The chromatin-remodeling complex WINAC targets a nuclear receptor to promoters and is impaired in Williams syndrome. *Cell.* 2003; 113:905–917. [PubMed: 12837248]
- Koszewski NJ, Henry KW, Lubert EJ, Gravatte H, Noonan DJ. Use of a modified yeast one-hybrid screen to identify BAF60a interactions with the Vitamin D receptor heterodimer. *J. Steroid Biochem. Mol. Biol.* 2003; 87:223–231. [PubMed: 14698202]
- Lemon B, Inouye C, King DS, Tjian R. Selectivity of chromatin-remodelling cofactors for ligand-activated transcription. *Nature.* 2001; 414:924–928. [PubMed: 11780067]
- Morillon A, Karabetsov N, O'Sullivan J, Kent N, Proudfoot N, Mellor J. Isw1 chromatin remodeling ATPase coordinates transcription elongation and termination by RNA polymerase II. *Cell.* 2003; 115:425–435. [PubMed: 14622597]
- Muchardt C, Yaniv M. A human homologue of *Saccharomyces cerevisiae* SNF2/SWI2 and *Drosophila* brm genes potentiates transcriptional activation by the glucocorticoid receptor. *EMBO J.* 1993; 12:4279–4290. [PubMed: 8223438]
- Narlikar GJ, Phelan ML, Kingston RE. Generation and interconversion of multiple distinct nucleosomal states as a mechanism for catalyzing chromatin fluidity. *Mol. Cell.* 2001; 8:1219–1230. [PubMed: 11779498]
- Neely KE, Workman JL. The complexity of chromatin remodeling and its links to cancer. *Biochim. Biophys. Acta.* 2002; 1603:19–29. [PubMed: 12242108]
- Nie Z, Xue Y, Yang D, Zhou S, Deroo BJ, Archer TK, Wang W. A specificity and targeting subunit of a human SWI/SNF family-related chromatin-remodeling complex. *Mol. Cell Biol.* 2000; 20:8879–8888. [PubMed: 11073988]
- Peterson CL, Workman JL. Promoter targeting and chromatin remodeling by the SWI/SNF complex. *Curr. Opin. Genet. Dev.* 2000; 10:187–192. [PubMed: 10753786]
- Phelan ML, Sif S, Narlikar GJ, Kingston RE. Reconstitution of a core chromatin remodeling complex from SWI/SNF subunits. *Mol. Cell.* 1999; 3:247–253. [PubMed: 10078207]
- Sif S. ATP-dependent nucleosome remodeling complexes: enzymes tailored to deal with chromatin. *J. Cell. Biochem.* 2004; 91:1087–1098. [PubMed: 15048866]
- Sims RJ 3rd, Belotserkovskaya R, Reinberg D. Elongation by RNA polymerase II: the short and long of it. *Genes Dev.* 2004; 18:2437–2468. [PubMed: 15489290]
- Trotter KW, Archer TK. Reconstitution of glucocorticoid receptor-dependent transcription in vivo. *Mol. Cell Biol.* 2004; 24:3347–3358. [PubMed: 15060156]
- Wade PA. Methyl CpG binding proteins: coupling chromatin architecture to gene regulation. *Oncogene.* 2001; 20:3166–3173. [PubMed: 11420733]
- Wan Y, Nordeen SK. Overlapping but distinct profiles of gene expression elicited by glucocorticoids and progestins. *Recent Prog. Horm. Res.* 2003; 58:199–226. [PubMed: 12795420]
- Wang JC, Derynck MK, Nonaka DF, Khodabakhsh DB, Haqq C, Yamamoto KR. Chromatin immunoprecipitation (ChIP) scanning identifies primary glucocorticoid receptor target genes. *Proc. Natl. Acad. Sci. U.S.A.* 2004; 101:15603–15608. [PubMed: 15501915]

- Wang W, Cote J, Xue Y, Zhou S, Khavari PA, Biggar SR, Muchardt C, Kalpana GV, Goff SP, Yaniv M, Workman JL, Crabtree GR. Purification and biochemical heterogeneity of the mammalian SWI-SNF complex. *EMBO J.* 1996a; 15:5370–5382. [PubMed: 8895581]
- Wang W, Xue Y, Zhou S, Kuo A, Cairns BR, Crabtree GR. Diversity and specialization of mammalian SWI/SNF complexes. *Genes Dev.* 1996b; 10:2117–2130. [PubMed: 8804307]
- Wolffe AP, Hansen JC. Nuclear visions: functional flexibility from structural instability. *Cell.* 2001; 104:631–634. [PubMed: 11257215]
- Xue Y, Canman JC, Lee CS, Nie Z, Yang D, Moreno GT, Young MK, Salmon ED, Wang W. The human SWI/SNF-B chromatin-remodeling complex is related to yeast rsc and localizes at kinetochores of mitotic chromosomes. *Proc. Natl. Acad. Sci. U.S.A.* 2000; 97:13015–13020. [PubMed: 11078522]
- Yan Z, Cui K, Murray DM, Ling C, Xue Y, Gerstein A, Parsons R, Zhao K, Wang W. PBAF chromatin-remodeling complex requires a novel specificity subunit, BAF200, to regulate expression of selective interferon-responsive genes. *Genes Dev.* 2005; 19:1662–1667. [PubMed: 15985610]
- Yoshinaga SK, Peterson CL, Herskowitz I, Yamamoto KR. Roles of SWI1, SWI2, and SWI3 proteins for transcriptional enhancement by steroid receptors. *Science.* 1992; 258:1598–1604. [PubMed: 1360703]
- Zhang Y. Transcriptional regulation by histone ubiquitination and deubiquitination. *Genes Dev.* 2003; 17:2733–2740. [PubMed: 14630937]

Fig. 1.

(A) The core SWI/SNF subunits are present within distinct remodeling complexes, BAF or PBAF, and can associate with several chromatin modifying complexes including histone modifying enzymes, transcription co-factors, and tumor suppressor complexes (i.e. NUMAC, WINAC, and NCoR). Nuclear receptors have been found to interact directly with BAF250, BAF60a, and BAF57. (B) Schematic representation of the MMTV organized as chromatin. The promoter, organized into six positioned nucleosomes (A–F), contains hormone-responsive elements, found within the nucleosome-B region, which become hypersensitive upon hormone treatment allowing for the recruitment of NRs.

Fig. 2.

Comparison of the ability of BRG1, SNF2h and B-S-B chimeric fusion protein to induce GR-dependent transcription from a MMTV chromatin template. NR-mediated transcriptional activation is a dynamic process involving recruitment of gene specific co-regulators to target promoters. GR-mediated transcriptional initiation of MMTV requires BRG1 ATPase activity. This activity cannot be substituted by other chromatin remodeling proteins present, such as SNF2h, or by the SNF2h ATPase found within a BRG1-SNF2h chimeric protein. These observations suggest NR-mediated transcriptional activation is a dynamic process dependent on a variety of functionally diverse co-regulators which appear to be receptor-, ligand-, and/or promoter-specific.