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Review

Chromatin remodeling during glucocorticoid receptor regulated transactivation ☆

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ABSTRACT

Steroid hormone receptor (SR) signaling leads to widespread changes in gene expression, and aberrant SR signaling can lead to malignancies including breast, prostate, and lung cancers. Chromatin remodeling is an essential component of SR signaling, and defining the process of chromatin and nucleosome remodeling during signaling is critical to the continued development of related therapies. The glucocorticoid receptor (GR) is a key SR that activates numerous promoters including the well defined MMTV promoter. The activation of MMTV by GR provides an excellent model for teasing apart the sequence of events between hormone treatment and changes in gene expression. Comparing hormone-induced transcription from stably integrated promoters with defined nucleosomal structure to that from transiently expressed, unstructured promoters permits key distinctions between interactions that require remodeling and those that do not. The importance of co-activators and histone modifications prior to remodeling and the formation of the preinitiation complex that follows can also be clarified by defining key transition points in the propagation of hormonal signals. Combined with detailed mapping of proteins along the promoter, a temporal and spatial understanding of the signaling and remodeling processes begins to emerge. In this review, we examine SR signaling with a focus on GR activation of the MMTV promoter. We also discuss the ATP-dependent remodeling complex SWI/SNF, which provides the necessary remodeling activity during GR signaling and interacts with several SRs. BRG1, the central ATPase of SWI/SNF, also interacts with a set of BAF proteins that help determine the specialized function and fine-tuned regulation of BRG1 remodeling activity. BRG1 regulation comes from its own subdomains as well as its interactive partners. In particular, the HSA domain region of BRG1 and unique features of its ATPase homology appear to play key roles in regulating remodeling function. Details of the inter-workings of this chromatin remodeling protein continue to be revealed and promise to improve our understanding of the mechanism of chromatin remodeling during steroid hormone signaling. This article is part of a Special Issue entitled: Chromatin in time and space.

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1. Introduction

1.1. Chromatin

In eukaryotes, changes in gene expression are regulated not only by interactions between DNA and transcription factors but also by DNA accessibility. DNA wraps around histone octamers to form nucleosomes, the basic units of chromatin, and nucleosomes are further packed into condensed chromatin fibers [1,2]. Each nucleosome contains approximately 146 base pairs of DNA and two copies each of histones H2A, H2B, H3, and H4 [1,2]. Favorable electrostatic interactions between the acidic phosphodiester backbone of DNA and the basic surfaces of the histone octamer lead to the formation of the nucleosome core particle, along with hydrogen bonding between histones and DNA phosphates and non-polar contacts between histones and DNA deoxyribose groups [3]. Between nucleosomes, stretches of DNA bind the linker histone H1, which stabilizes chromatin and compacts 10 nm strands of nucleosomes into higher order 30 nm and 100 nm fibers that can ultimately form chromosomes [4–7]. Not only does this system allow cells to pack almost 2 m of DNA into a sphere with a radius of a few micrometers, it also regulates access to DNA. Densely packed chromatin can repress transcription and other processes that require protein–DNA interactions, such as replication, recombination, and repair [8–10]. In this manner, chromatin introduces a system for regulating gene expression and other DNA-dependent processes based on the interactions between DNA and histones that position nucleosomes and underlie chromatin structure.

1.2. Histone modifying and chromatin remodeling complexes

Several biological processes in eukaryotes are dedicated to modulating chromatin structure [11,12]. The two major classes of chromatin remodeling/modifying complexes are the ATP-dependent remodelers and the histone modifying remodelers. While ATP-

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dependent remodelers mechanically separate DNA–histone contacts using the energy of ATP hydrolysis, histone modifying chromatin remodelers posttranslationally "mark" histone tails that protrude from nucleosomes. Histone marks include acetylation, phosphorylation, methylation, ubiquitination, and other covalent modifications that allow the tails to act as binding surfaces, often for chromatin-modifying factors and complexes [12,13]. These modifications do not substantially impact the nucleosome core particle structure, but do affect higher order chromatin structure and gene expression [14–16].

The relationship between transcriptional activation and histone acetylation was established over 50 years ago, after it was observed that acetylation of histones results in increased transcription [17]. Since then, associations between specific histone marks and changes in transcription have been the focus of numerous investigations and led to the development of a histone code hypothesis [18,19]. The extensive study of acetylation at specific lysine residues along histone tails has demonstrated how the histone acetylases (HATs) that catalyze this modification loosen chromatin by replacing a positively charged residue with a negatively charged functional group, reducing DNA–histone affinity and leading to increased transcription [20,21]. This activating mark can be removed by histone deacetylases (HDACs), establishing a dynamic process that plays a key role in regulating gene expression. Many proteins involved in steroid hormone stimulated transcriptional activation have HAT activity, while repressors are associated with HDAC function [14].

Although acetylation is generally associated with active transcription, the effects of other histone tail modifications are more complex. Methylation, for example, can both enhance and repress transcription [18]. The context-specific consequences of individual marks as well as the importance of neighboring histone tail modifications in directing interactions between nucleosomes and additional histone modifying complexes leads to the complex "code" that continues to be characterized [13,18,22]. One mark of particular interest in hormone inducible transcriptional activation is histone H1 phosphorylation, which is required for active transcription from the GR-inducible MMTV promoter and is discussed further in Section 3.2 of this review [23–28]. The impact of histone structure and biochemistry on gene expression can also be observed in the effects of variant histones, which can replace each of the core histones and H1 [11,29]. Subtle structural differences in variant histones, like changes that occur through tail modifications, are associated with changes in both chromatin structure and gene expression [29]. The impact of histone modifications on gene expression demonstrates one system of regulation based on manipulating the structure of chromatin. Another system for gene regulation through chromatin remodeling comes from the direct mechanical action of ATPase-driven chromatin remodeling complexes, which often work in concert with histone modifying complexes to regulate transcription and other DNA-dependent processes in response to biological events and signals [30].

1.3. ATP-dependent chromatin remodeling complexes

ATP-dependent remodeling complexes work by directly breaking histone–DNA contacts to slide and reposition nucleosomes [31,32]. To separate bonds between histones and DNA, the ATP-dependent class of remodelers uses energy derived from ATP hydrolysis, which is carried out by a central ATPase subunit. These proteins come from the SF2 helicase superfamily, which shares a structural core consisting of two RecA helicase-like domains that bind and hydrolyze ATP [33,34]. Within SF2 superfamily, the Snf2 family includes five major families of ATP-dependent remodelers including SWI/SNF, ISWI, Mi-2/NuRD, INO80, and SWR1 as well as the repair and recombination proteins RAD16, ERCC6 and RAD54 [35,36]. The central ATPase domain region of Snf2 proteins consists of paired DEXHc and HELICc domains which include subregions of strong homology [37]. In addition to the ATPase domain, other common domains and motifs are found among Snf2 proteins. Some of these domains are known to interact with histones (BROMO, CHROMO, SANT) and to bind DNA (AT hook, Zn finger), while others have functions less well defined (HSA, BRK) but which may be important for protein–protein interactions [38–40]. Yeast SWI2/SNF2 (mating type SWItching defective/Sucrose Non Fermenting) was the first Snf2 remodeler to be discovered through genetic studies that initially demonstrated roles in mating-type switching and sucrose fermentation [41]. These effects were later attributed to a role in opposing the inhibitory effect of chromatin [42,43]. Biochemical assays revealed SWI2/SNF2 forms a large protein complex and remodels nucleosomes in an ATP-dependent manner [44,45]. The human homologues of yeast SWI/SNF proteins have been identified through sequence homology and shown to similarly form complexes and remodel chromatin in an ATP-dependent manner [46,47].

1.4. BRG1, the central ATPase of SWI/SNF

In humans and other mammals, SWI/SNF can have one of two possible ATPase core subunits, BRG1 or BRM [48–50]. These ATPases have significant sequence homology yet non-redundant roles. Loss of BRG1 is lethal prior to embryonic implantation in mice, and BRM cannot compensate for its loss [51–53]. BRG1 can compensate for BRM, however, suggesting a BRG1-specific role that is critical during development. Furthermore, murine embryos heterozygous for a BRG1 null mutation are predisposed to form tumors [51]. In humans, BRG1 mutations have been observed in a variety of tumor cells [54–59]. More recently, BRG1 has been identified as critical for inducing and maintaining cellular pluripotency [60,61]. The domain structure of BRG1, the functions of individual BRG1 subdomains, and the importance of BRG1 protein–protein interactions in the context of hormone dependent, BRG1-mediated transcriptional regulation will be discussed in greater detail in Section 3.

1.5. SWI/SNF complex subunits

The BRG1 ATPase is found in complex with several subunits termed BRG1 associated factors (BAFs) that form a highly regulated, multifunctional complexes. Some human BAFs have direct yeast orthologs; these include BAF170, BAF155, BAF60, BAF53, and BAF47. Other BAFs are unique to the mammalian complex, and these are BAF57, BAF45, BAF250, BAF200, and BAF180/Polybromo. B-actin, Brd7, and Brd9 are also subunits of SWI/SNF complexes [62]. BRG1 is found in remodeling complexes other than SWI/SNF, as well, including NUMAC, WINAC, NCoR, and mSin3A/HDAC complexes [50]. Many BAFs also appear in these complexes, which are associated with chromatin dependent processes such as transcription, elongation, and DNA replication. Other than B-actin, the only component of SWI/SNF found in a complex that does not contain BRG1 is BAF53, which is also found in the INO80 remodeling complex [63]. While some BAF proteins appear in all SWI/SNF complexes, others are changeable [64–68]. The list of "core" BAFs has changed over time as new SWI/SNF complexes that exclude certain subunits or include new subunits are discovered, although BAF155, BAF57, BAF47, and BAF53 are still considered essential [49,68]. The first major distinction between SWI/SNF subtypes came with the discovery that BAF250 and BAF180 are not found in the same complexes, formulating the BAF (BAF250-containing) and PBAF (BAF180-containing) subclasses of SWI/SNF [65]. Brd7 and BAF200 are only associated with PBAF complexes, and BRM, the close and typically interchangeable homolog of BRG1, is not found PBAFs [66,67]. Additionally, BAF170 is not found in SWI/SNF complexes purified from mouse embryonic stem cells (esBAFs), and, like pBAFs, esBAFs contain only BRG1 and not BRM [68].

Different SWI/SNF configurations have been associated with different functions during heat shock and immune responses. BRM-