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Review Article

Chromatin Remodeling Complexes: The Regulators of Genome Function

Abstract

Genome in eukaryotes is large enough to be accommodated in tiny nucleus. It is required to achieve high degree of compaction for getting into the nucleus. Compaction is achieved by folding the DNA in the form of chromatin. But chromatin acts as general repressor for the entire genomic functions. Therefore, it requires being selectively unpacked for gene expression. However this packing and unpacking of chromatin need to temporally and spatially regulated for differential regulation of genomic functions like DNA replication, repair, recombination and transcription. Chromatin remodeling factors regulate structure and function of chromatin in time and space to facilitate various genomic functions. Chromatin remodeling complexes can be broadly categorized into those that carry out remodeling by utilizing energy from ATP hydrolysis and those that covalently modify chromatin proteins and thus bring about permanent yet reversible alteration in the chromatin structure.

Introduction

Living organisms are improbable steady-state systems. They exist in environment that changes from seconds to minute, day to day and over the years and centuries. If we ask what enables them to continue on this unlikely course, the answer will be "information" that they inherit in their genetic material, which allows them to take actions to prevent death. They can do this on various scales. Every organism is an agent selecting from time to time what is best to do in the changing circumstances. An organism can choose 'wisely' because its 'genome' provides it with receptors tuned to respond to changes that are likely to occur. Such a diploid genome in case of human is about 2 meters long and must be compacted to fit into a nucleus with diameter that is about 200,000 fold smaller. And the situation is quite similar in other eukaryotes. Eukaryotic cells have solved this packaging problem by folding their DNA along with protein into a highly compacted structure called 'chromatin' [1].

Chromatin: A solution and the problem

All the chromatin proteins may be divided into two categories; histones and non-histone protein. This distinction is based on unique characteristics and functions of histones. Their relative amounts and stoichiometry with respect to DNA are nearly constant throughout the eukaryotic kingdom. Histone proteins form a core around which DNA is tightly wrapped forming 'nucleosome', the structural unit of chromatin. Biochemical and genetic experiments over the past

two and a half decade have confirmed that the organization of eukaryotic DNA in chromatin exerts a general repressive effect on replicative and transcriptional processes [2]. Therefore after solving the problem of packaging the genome, chromatin structure give rise to another problem of accessibility of the genome by various processes requiring DNA as the substrate.

Replicative and transcriptional processes therefore require the chromatin to be differentially unpacked and subsequently packaged, with minute temporal and spatial precision. One of the most intriguing phenomena related to chromatin structural variability is the presence of two morphologically different types of chromatin within a single inter-phase nucleus: the dispersed euchromatin and condensed heterochromatin. The nature of replicative and transcriptional mechanics *in vivo* poses a tough challenge to our understanding, about how the chromatin condensation (and decondensation) is accomplished. Even though we know very little about the mechanism and nature of higher-order chromatin folding and unfolding, the chromatin changes at a simpler (nucleosomal) level of organization have been unraveled [1]. The X-ray crystal structure of both the histone octamer and the nucleosome core particles have been obtained at high resolution. During the past several years these structures have served as the primary basis for interpreting nucleosome function in chromatin fibers. The nucleosome [3-5] is made up of an octamer of four core-histones H2A, H2B, H3 and H4 around which about 147 bp of DNA wraps 1.65 left handed superhelical turns, assuming a molecular mass of ~206 kDa.

Different DNA binding proteins are affected differentially by the nucleosomal DNA. A common finding too many DNA binding proteins is that if its cognate DNA binding site is located close to nucleosome border then it is more accessible than the same DNA site located close to the nucleosomal dyad [6]. One extreme is nuclear factor NF1 which has 100–300 fold reduced affinity for its nucleosomal site compared to free DNA, independent of translational and rotational positioning. It should be noted however, that a rotationally unfavorable positioned DNA element where the factor binding surface, forming the base specific protein contacts, is facing towards the histone octamer, in most cases, usually has drastically lower accessibility, than if this surface is positioned away from the histone surface [7].

Nucleosomes are not structurally inert but instead undergo several conformational transitions that are dynamic and likely to be important *in vivo*. At molecular level nucleosomal DNA exist in dynamic equilibrium between wound and unwound state to the histone octamer [8,9]. This dynamic behavior exposes DNA sites with a probability of 1 in 10³ to 10⁵ as one moves from periphery towards the centre, so the apparent DNA binding affinities of many *trans* acting factors for nucleosomal DNA simply will be reduced by 10³ to 10⁵ fold compared with the affinities of these factors for the same site on naked DNA. Thus, although the time averaged fraction of nucleosomes with exposed binding site is small, factors having sufficiently high affinity for naked DNA and/or present in locally high concentration will still be able to bind to their cognate element in chromatin, as dictated by laws of mass action.

Chromatin remodeling complexes: A solution to the problem

It is evident that structure of nucleosome described above renders nucleosomal DNA less accessible. One molecular solution to the problem of chromatin restructuring is provided by the activities of chromatin remodeling factors [Figure 1]. Two classes of chromatin remodeling factors have been described.

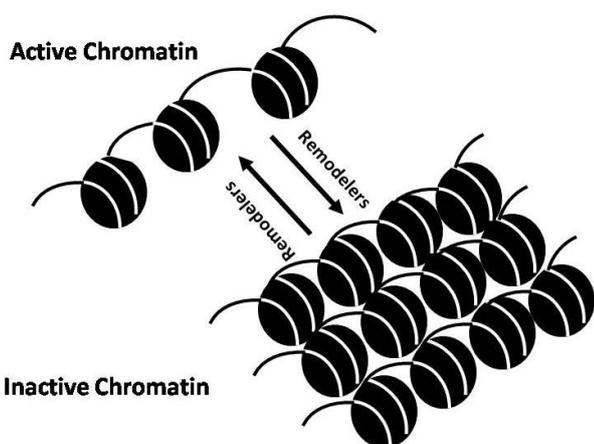


Figure 1: Active chromatin is decondensed to the extent that DNA binding factors can get access to DNA binding sites. Inactive chromatin is condensed and compact structure refractory to DNA binding factor. These two forms are temporally and spatially inter convertible by orchestra of various chromatin remodeling factors, including ATP dependent remodelers and chromatin modifiers.

First class of chromatin remodeling factors includes protein complexes that bring about alteration in the chromatin structure by covalently modifying histones. Whereas second class remodeling complexes are of molecular motors, the ATP-dependent chromatin remodeling factors [10].

ATP-independent chromatin remodeling

ATP-independent chromatin remodeling is brought about by factors that are responsible for posttranslational, covalent modifications in various histones. Large number of elegant review articles published recently, provide in depth analysis of composition and its functional implication of histone modifying complexes [11]. However, in order to stay focused on the theme of this thesis, chromatin remodeling by various modifications of chromatin, have been briefly addressed below.

Chromatin remodeling by chromatin modifications

The core histones that make up nucleosome are subject to more than 100 different post translational modifications: acetylation [11], methylation [12] phosphorylation, ADP ribosylation and ubiquitilation [11,13]. These occur primarily at specific positions within the non-globular amino-terminal histone tails which protrude from the core of the nucleosome (explained above). Since they were discovered in 1960's histone modifications have been predicted to affect all aspects of chromosome biology, including transcription, replication, recombination and condensation, by affecting chromosome structure and by recruiting specific chromatin-binding proteins.

There have seen considerable progress in understanding of acetylation and methylation of lysine residues in the histones. On a genome wide basis, histone H3 K4 tri-methylation and H3K9 acetylation are associated with active transcriptional start sites. Phosphorylated H2A.X foci mark sites of DNA damage and methylation of Histone H3 Lys9 recruits chromodomain-containing proteins, such as heterochromatin protein 1 (HP1) [14]. Acetylation of lysine residue in histone octamer almost always correlates with chromatin accessibility and transcriptional activity; and that the functional importance of acetylation depends completely on the accuracy and efficiency of the reverse reaction, histone deacetylation. One of the way in which modifications such as acetylation affect transcription is based on the recruitment of activators due to recognition via modification binding domain for example acetylation of histones recruits bromodomain-containing proteins [15–17]. However, recent advances in the methylation related studies indicate that lysine methylation can have different effects depending on which residue is modified. Methylation, in particular, was linked to the regulation of gene expression and chromatin conformation [18,19]. Most modifications are dynamic. Although histone methylation was long considered irreversible, the recent identification of numerous site-specific histone demethylases provides compelling evidence that this modification is dynamically regulated [20]. A flurry of recent studies has offered glimpses into the specific biological roles of the histone modifying enzymes and their potential connections to human diseases [20]. Of all the enzymes that modify histones, methyl transferase and kinases are the most specific.

There are two characterized mechanisms for the function of modifications. The first is disruption of contacts between nucleosomes in order to unravel chromatin and second is the recruitment of non-histone proteins. Second one is the most characterized till date. Thus depending upon the composition of modifications (histone code) on a given histone a set of proteins are encouraged to bind or are occluded from chromatin. These proteins carry with them enzymatic activities (i.e. remodeling ATPases) that further modify chromatin. The need to recruit an ordered series of enzymatic activities comes from the fact that processes regulated by modifications (transcription, replication, repair) have several steps. Each one of these steps may require a distinct type of chromatin remodeling activity and a different set of modifications to recruit them [11].

ATP dependent chromatin remodeling

ATP dependent chromatin remodeling is brought about by the factors called remodelers. Remodelers are DNA dependent motors that utilize energy derived from ATP hydrolysis to non-covalently alter this structure [21,22]. These enzymes are member of a diverse group of proteins named (SWI/SNF) after the archetypal *S. Cerevisiae* Snf2 proteins; the Snf2 family. Multiple members of this protein family are present in the sequenced genomes of eukaryotes, of which the chromatin remodeling enzymes form distinct sub groupings [23]. The crystal structure of catalytic domains of the two Snf2 related proteins highlight structural similarities with the RecA domain found in the range of helicases [24]. Snf2 proteins use the energy of ATP hydrolysis to alter the histone DNA interaction. However, unlike *bona-fide* helicases, the action of chromatin remodeling enzymes are not generally associated with separation of DNA strands.

Remodelers can *in vitro* mediate (a) nucleosome sliding, in which the position of nucleosome on DNA changes, (b) the creation of a remodeled state, in which DNA becomes more accessible but histones remain bound, (c) complete dissociation of histone and DNA, or (d) histone replacement with variant histones (for a detailed discussion see below). At the same time, ATP dependent remodelers work in conjunction with histone chaperones and histone modifying enzymes [25].

Currently, four different classes of ATP-dependent remodeling complexes can be recognized: SWI/SNF, ISWI, Mi-2, and Ino80. Each class is defined by the presence of a distinct ATPase [10].

SWI/SNF group

Historically, it was the discovery of yeast SWI/SNF complexes in the mid-1980s initiated spurt in studies of chromatin remodeling. First chromatin remodeling complex was purified from yeast. It is product of five SWI and SNF gene (SWI1, SWI2/SNF2, SWI3, SNF5 and SNF6) were found to be constituents of a 2 MDa complex [26,27] named SWI/SNF complex. Later on affinity-purified complex contained, in addition to SWI1, SWI2/SNF2, SWI3, SNF5 and SNF6, five more then-unknown proteins with molecular weights of 78, 68, 50, 47 & 25 kDa [28].

All prototype SWI/SNF-type complexes studied so far contain a minimal structural and functional core composed of four evolutionarily-conserved subunits: homolog of yeast proteins SWI2/SNF2 (the ATPase, major catalytic subunit), SNF5, SWI3 and SWP73 [29,30]. The complex has an ATPase activity that is stimulated by DNA (~30 fold) or by nucleosomes (~40 fold) [28]. Functional characterizations of the complex revealed that it could stimulate binding of GAL4 (and GAL4 derivatives) to nucleosomal binding sites in presence of ATP. In a mutated complex, wherein the SWI2/SNF2-NTP binding motif is rendered non-functional by a point mutation (K798→A), fails to stimulate activator binding to nucleosomes. This suggests that the ATPase activity of SWI2/SNF2 is essential for the SWI/SNF function, but is not needed for structural assembly of the complex. The complex was found (i) to bind DNA in a sequence-non-specific manner with preference for four-way junction DNA, (ii) to interact with DNA through the minor groove, and (iii) to induce positive supercoiling in relaxed plasmids in the presence of ATP [31]. The complex was however redundant when multiple transcription factors bind to nucleosomes *in vitro* [32]. Reportedly, the yeast SWI/SNF complex (i) disrupted a nucleosome in the presence of ATP, and (ii), persistently remodeled a specific GAL4-binding site-containing nucleosome along an array of nucleosomes in presence of ATP and GAL4, and (iii) evicted histones from activator-interactive nucleosomes in the presence of an activator [33]. In addition, the complex was found to slide nucleosome along a longer DNA fragment [34]. The available data indicate that the subunits have specific roles in determining the range of targets and biological functions of the complexes.

SWI/SNF group of remodelers can be further subdivided into two distinct highly conserved subclasses. One subfamily comprises yeast SWI/SNF, *Drosophila* BAP (Brm associated proteins) and mammalian BAF complex; whereas the second family includes yeast RSC, *Drosophila* PBAP, and mammalian PBAF complexes [Figure 2]. Chromatin remodeling activity although well-established across the animal phyla has also been reported in plant [35].

In animals, the subunits of SWI/SNF complexes are involved in key developmental pathways at both early and later stages of the life cycle. The mechanisms underlying this involvement include: (i) direct interactions with promoter- or enhancer-binding proteins [36], (ii) mediation of glucocorticoid- and stress-induced apoptosis [37], (iii) contribution to genomic recombination, e.g., during T-cell differentiation [38], (iv) physical interactions with components of signaling pathways, e.g., interactions of BRG1 ATPase with inositol, promoted association of SWI/SNF subunits with chromatin [39,40] and (v) promoting cell-cycle arrest, either by down regulation of E2F target genes, like cyclin E, or up-regulation of cyclin-dependent kinase inhibitors [41].

ISWI group

The first member of this growing group of chromatin remodeling complexes, dNURF, and dCHRAC were identified in *Drosophila* embryo extract using *in vitro* assays for activities allowing transcription factor access to sites in nucleosomal

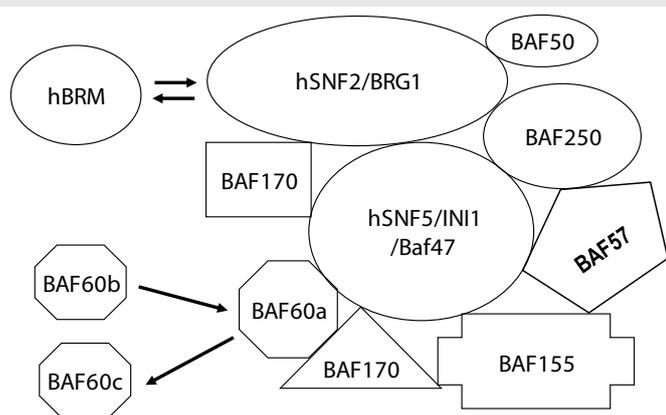


Figure 2: BAF complex. All the ATP dependent chromatin remodeling complexes from identified so far yeast to human are multi protein complexes. SWI/SNF homologue in human is called BAF (Brg Associated Factor) complex that contain about 10 subunits. The SNF2 homologue and ATPase subunit can be either BRG protein as in BAF complex or it can be hBRM as in PBAF complex. Tissue specific and developmental stage specific changes in compositional heterogeneity in the subunit of these complexes facilitate precise regulation of genomic functions.

and NRD (nucleosome remodelling and deacetylating) [55-57]. CHD4/Mi-2h and CHD3/Mi-2a are highly related proteins that are autoantigens in the human disease dermatomyositis. These proteins are ATPases and presumably lead to the ATP-dependent chromatin-remodeling activity of NURD complexes, and in fact recombinant human Mi-2 was found to have ATPase activity comparable to intact NuRD complex [58].

A Mi-2 homolog also exists in *Drosophila*, named dMi-2 that exists in a large complex, similar to its human and *Xenopus* counterparts, but this complex is much less characterized. It does seem to contain histone deacetylase activity. Some striking differences between recombinant dMi-2 and ISWI were found. The ATPase activity of dMi-2's ATPase is only stimulated by nucleosomes. Furthermore, dMi-2 was able to bind nucleosome cores (which presumably display no free DNA), and dMi-2 move histone octamers in opposite directions in a sliding assay, suggesting that in contrast to ISWI remodeling complexes aMi-2 use different mechanisms of nucleosome mobilization [53]

A complex highly homologous to the NURD complexes was isolated from *Xenopus* egg extracts that demonstrate histone deacetylase activity along with nucleosome-stimulated ATPase activity [59,60].

INO80.com

The *INO80* gene (*YGL150C*) was identified in a genetic screen for mutants affecting inositol biosynthesis [61]. The product of this gene is highly related to the DNA-dependent ATPases in the SNF2/SWI2 superfamily of chromatin remodeling complexes. The Wu group purified and characterized the INO80 complex.

The purified INO80 complex contains 15 principal subunits with roughly equivalent stoichiometry except for Rvb1 and Rvb2, which show 6:1 stoichiometry with other polypeptides [62]. INO80 complex is highly conserved in human INO80 complex contains orthologs of Ino80, Rvb1, Rvb2, Arp4, Arp5, Arp8, Ies2 and Ies6, as well as five unique subunits [63].

The *in vitro* biochemical studies showed that the INO80 complex has DNA-dependent ATPase activity, as well as 3'-5' helicase activity [62]. INO80.com was also found to be able to bind to free DNA with an apparent binding constant (~10 nM), which is comparable to that of SWI/SNF [64]. The INO80.com participates in multiple DNA repair pathways by its nucleosome remodeling ability and by regulating the accessibility of DNA repair proteins around the DSB site. Though the INO80 complex has been previously shown to play an important role in transcription, the recent finding on the roles of INO80 complex during the DNA damage response emphasizes the notion that chromatin remodeling complexes can be involved in distinctly different cellular processes [65]. DNA. INO80-C and RSC remodelers play important role in nucleosome eviction at DSB (double stranded breaks) and facilitate Rad51 binding [66]. Additionally INO80 and RSC both remodelers appear to contribute to end resection.

arrays [42,43]. Later multiple additional remodelers belonging to this group were identified in yeast [44], humans [45,46], mouse [47] and *Xenopus* [48]. The ATPase subunit of this group of remodeling complex was named Imitation switch (ISWI) because of its similarity to SWI2 ATPase in the SNF2 subfamily DEAD/H helicases. Characteristic of ISWI type ATPase is the presence of a SWI3, ADA2, N-CoR and TFIIB (SANT) domain and absence of a bromodomain [49]. These remodeling complexes have an ATPase subunit that belongs to the SWI2/SNF2 subfamily of DEAD/H helicases [50]. SANT-like domains in the catalytic subunit have been proposed to interact with histone tails [51,52]. The complexes in this group are relatively smaller (300-800kDa) and contain fewer subunits ranging from 2-4 as compared with larger complexes in the SNF2, CHD, and INO80 subfamilies which contain upto 15 subunits and are often ~2MDa.

CHD/Mi2 Group

In addition to having a Swi2/Snf2-like helicase/ATPase domain, members of the CHD subfamily also contain a chromo (chromatin organization modifier) domain and a DNA-binding domain [53]. Chromo domains are found in a number of proteins, including many that have the ability to interact with heterochromatin, such as *Drosophila* Polycomb, *Drosophila* HP1, *S. pombe* Clr4 histone methyltransferase (HMTase), *S. pombe* Swi6, and mammalian SUV39H1 HMTase. The mechanism by which chromo domains are brought to heterochromatin is unclear, but it may involve binding to methylated histones. Recently, chromo domains were found to act as recognition motifs for methylated lysine-9 of histone H3 [14]. Chromo domains have also been shown to interact with RNA as well as to self-associate with one another [54]. Many complexes that contain a CHD family member and that display both histone deacetylase and ATP-dependent nucleosome disruption activities were purified from both humans and *Xenopus laevis*. In humans, this complex was individually identified by three different laboratories, and named NURD (nucleosome remodeling and histone deacetylation), NuRD,

Conclusion and Future Perspective

This review discussed the problems posed by large size of genome in eukaryotes and its solution provided by packaging of the genome in the form of chromatin. However his packaging makes genome inaccessible to different factors that require DNA as substrate. For genome functions like replication, repair, recombination and transcription, it requires differential unpack aging of genomic chromatin. Eukaryotic cells have solved this problem by evolving chromatin remodeling enzymes and processes that regulate chromatin structure and differential gene expression in vivo. Many chromatin remodeling complexes from yeast, drosophila and human have been purified and characterized. Yet there are left many systems like bird and fishes where a remodeling complex is yet to be purified. On one hand it can help in bridging the gap that exist between identified remodeling complexes, while on the other hand it may lead to identification of novel subunits, their functions and regulation, that will add to the dynamicity of these complexes. Finally in human health chromatin remodeling can be used for diagnosis and prognosis of traits like current and the time course activity of disease.

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