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Review Article

CHROMATIN REMODELERS: ATP-DRIVEN MOTOR PROTEINS INDUCING GENE EXPRESSION

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ABSTRACT

The chromatin-based structure dynamics are crucial for the regulation of gene expression, gene transcription and chromosomal functions. Chromatin remodelers are the major types of ATP-driven motor proteins that moves along the DNA, gain energy from ATP hydrolysis, and use DNA as a 'Rail' to act on chromatin. The primary key role of these chromatin remodeling enzymes is to take part in the dynamic changes in chromatin structure during cellular processes, including gene transcription, DNA repair, recombination, and replication. Recent biochemical studies demonstrated that loss of these enzymes can cause global transcriptional defects alters higher-order chromatin structure.

Keywords: *Chromatin remodelers, nucleosome, motor proteins, gene expression, SWI/SNF, ISWI*

Introduction

Motor proteins are specific kinds of nano-machines that move along cytoskeletal filaments by a mechanism where energy is gained from the hydrolysis of ATP (Pollard *et al*., 1974). By hydrolyzing the ATP and controlling the release of inorganic phosphate, they can generate mechano-chemical forces that can be utilized for some of the key physiological and physiochemical roles of cell regulations (Hwang *et al*., 2009; Brenner 2001). On the basis of the substrates, motor proteins can be categorized into three major families (Goedert *et al*., 1991). Myosin is one of the major super families of ATP-driven motor proteins responsible for muscle contraction in striated muscle tissue and smooth muscle tissue (Pollard *et al*., 1973). Upon gaining energy from ATP hydrolysis, myosin is coupled with actin and based on this interaction; muscle contraction has been regulated (Guhathakurta *et al*., 2018). Kinesin is another ATP-dependent nano-machine that has crucial physiological roles in cell division, mitosis and meiosis, intracellular transport alongside signal transduction (Maruta *et al*., 2004; Endow 2003). Previous structural analysis has shown interesting similarities between the structures of the catalytic domain of myosin, kinesin and G-proteins, which suggests an ordinary common ancestor (Shibuya *et al*., 2002). This relation provides the insight that these motor proteins use the same kind of conformational strategy at the first stage of energy transduction through ATP hydrolysis

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and act as a molecular switch (Heuston *et al*., 2010). Recently discovered ATP-driven motor proteins, which are chromatin remodelers, could act upon nucleosomes (Hauer *et al*., 2017). Previous studies have revealed that ATP-dependent chromatin-remodeling enzymes can act as regulators of almost all of the chromosomal processes inside the cells and the deregulation of these enzymes might lead to a variety of diseases, including cancer (Hasan *et al*., 2019).

Chromatin Remodelers: The Enzymes that Target Chromatin

All the DNA-dependent processes are based on chromatin's structure and functions, the packaged form of the eukaryotic genome (Jang *et al*., 2019).Chromatin is composed of nucleosome which is made up of histone octamer around which DNA is wrapped. The histone octamer has two H2A and H2B, H3 and H4 (Stephens *et al.*, 2019). Together with that 8 histone nucleoproteins and a 147 base pairs of DNA make the chromatin's nucleosomal core (Babokhov *et al.*, 2020). It has been well-studied and well-established that histone is acting as the regulator for the regulation of transcription into cells (Fierz *et al*., 2019). Most of the nucleosome assembly happens during DNA replication and recombination and thus enables the delivery of histones to nascent DNA by histone chaperons. Recent studies revealed that a couple of protein complexes can take part in transcription and regulate gene expression through the modification or alteration of chromatin structure (Sacharowski *et al*., 2019).

The mechanism by which the position, occupancy, or histone composition of a nucleosome in chromatin is altered is known as chromatin remodeling (Manelyte *et al*., 2013). Chromatin remodeling is not a build-in character of transcriptional activators; instead the activators hire specialized enzymes that complete all of the chromatin remodeling events. These enzymes are considered as chromatin remodeling enzymes (Vignali *et al*., 2000; Fry *et al*., 2001). Chromatin remodeling enzymes utilize energy gained by ATP hydrolysis (~7.3 kcal/mole) to alter the nucleosome, which is the chromatin's building block and involves in all processes occurring on DNA (Becker *et al*., 2002). Chromatin remodeling enzymes can be called multi-protein assemblies containing an ATPase subunit which can mobilize the nucleosomes by using the energy gained from the hydrolysis of ATP altering the chromatin structure (Längst *et al.*, 2015). They are ATP-dependent factors that reposition nucleosomes to create euchromatin and heterochromatin states (Haokip *et al*., 2016). Each member of the ATP-dependent chromatin remodeling enzyme contains an ATPase subunit which relates to the SWI2/SNF2 subfamily (Eisen *et al*., 1995).

Families of Chromatin Remodelers

Based on the functions and on the similarities or dissimilarities in the catalytic ATPases and inserted subunits, chromatin remodeling enzymes can be classified into four subfamilies associated with gene expression (Fig. 1) (Zhou *et al*., 2016). The ATPase domain, which is conserved in all of the chromatin remodelers, made up of two RecA-like folds that are DExx and HELICc.

(a) First family: ISWI (Imitation SWItch)

The first family of chromatin remodeler is the ISWI family (Imitation SWItch), mainly involved in gene transcriptional repression and activation by catalyzing nucleosome spacing and compacting of higher order structures of chromatin. ISWI ATPase gene was first discovered in

Drosophila and is present in several chromatin remodeling complexes such as NURF, CHRAC and ACF (Elfring *et al*., 1994). ISWI complexes composed of 2-4 subunits where each has the nucleosome-dependent ATPase ISWI (Tyagi *et al*., 2016).

(b) Second family: CHD (Chromodomain-Helicase DNA binding)

Alongside ISWI, CHD (Chromodomain-Helicase DNA binding) is another major type that promotes gene transcription by moving or ejecting the nucleosome from the chromosome (Zhang *et al*., 2016). CHD family constitutes a major group of chromatin remodelers and thus further categorized into 3 subfamilies (Hall *et al*., 2007). Combination of CHD and ISWI is also defined as nucleosome-spacing enzymes needed to maintain the nucleosomal organization.

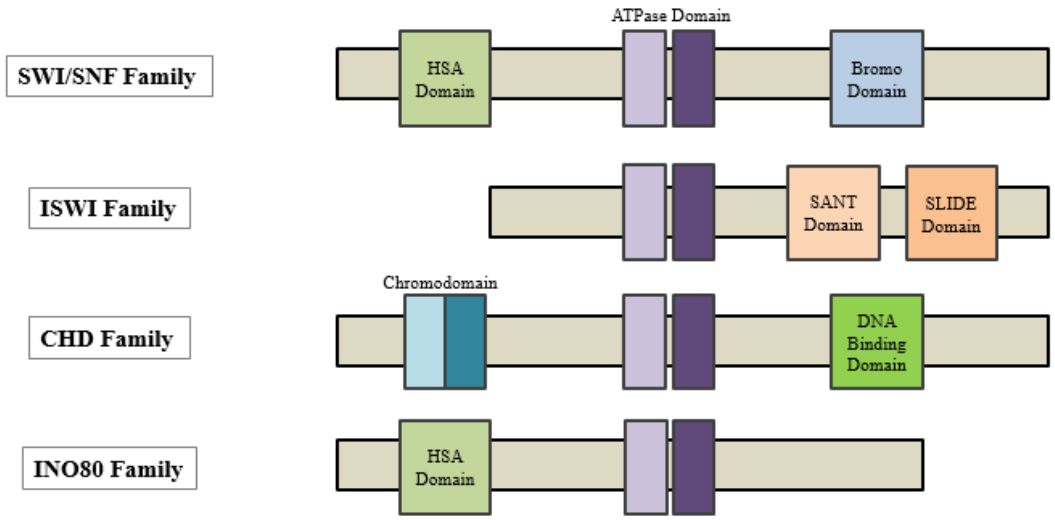

Fig. 1. Families and domain organization of chromatin remodelers. Basic structural organization of the four families of chromatin remodeling enzyme: SWI, ISWI, CHD and INO80. All of them have a common RecA-like ATPase subunit that is consists of ATPase Lobe-1 and Lobe-2 region, connected by a small flexible liker. Other structural features include a chromodomainin CHD whereas, SWI and ISWI have bromodomain and SANT-SLIDE domain, respectively.

(c) Third family: SWI/SNF (SWItching defective/Sucrose Non-Fermenting)

Recent Studies showed that another type of chromatin remodeling enzyme called SWI/SNF (SWItching defective/Sucrose Non-Fermenting) corresponds to genes encoding histones and other chromatin proteins (Vignali *et al*., 2000). This subfamily of chromatin remodeler functions by sliding or ejecting nucleosomes, removing histones from DNA, and thus participates in gene activation or repression.

(d) Fourth family: INO80 (Inositol requiring 80)

Lastly, INO80 (Inositol requiring 80) family of enzyme remodelers exhibits DNA helicase activity by binding to specialized DNA structures. It is identified that they even show additional function in DNA repair through homologous recombination. INO80 and SWR1 were demonstrated histone-exchange activity and have the ability to replace nucleosomal H2A.Z/H2B with free H2A/H2B dimers (Oberbeckmann *et al*., 2021).

Basic Mechanism of Action of Chromatin Remodelers

The chromatin remodelers share a common mechanism of action with other ATP-driven motor proteins such as myosin and kinesin. All types of chromatin remodelers' act by a shared DNA translocation mechanism to provide the force required to break the histone-DNA contacts. Since they all have a conserved ATPase motif which consists of two RecA-like lobes, the common DNA translocation mechanism between them is reasonable. Even though the molecular mechanism of DNA translocation by chromatin remodeler is still obscure, several well-studied experimental data showed the insight. Some of those are based on direct assays that provide real-time strategic data while others are indirect assays that test translocation and the effect of remodelers on DNA or nucleosome. The DNA translocation of chromatin remodelers can be called as 'inchworming' mechanism (Clapier *et al.*, 2017). During the translocation, helicases insert a protein domain between the two DNA strands that leads to the separation of DNA strand. Together with the DNA-binding cleft, the site for ATP binding and hydrolysis between the RecA-like lobes constitute the DNA translocation motor (Qiu *et al.*, 2017). These two lobes then bind to the same strand of the DNA, but one lobe is positioned slightly ahead than other. By this way, they create a unidirectional movement. By this mechanism the two RecA-like lobes act like reciprocal unit that sequentially bind to and release DNA which is similar to two 'mittens' moving approximately 1-2 base pair of DNA per cycle of ATP binding-hydrolysis-release (Fig. 2).

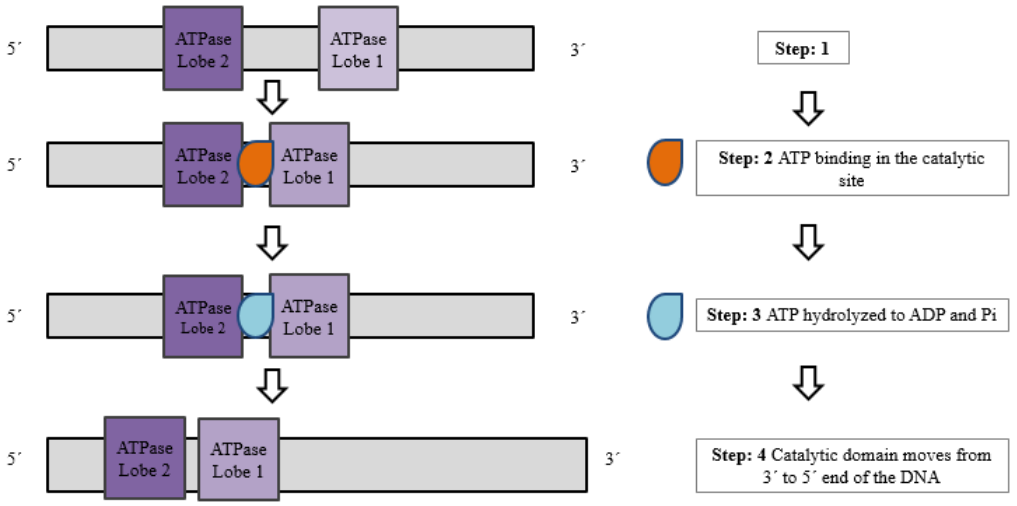

Fig. 2. Schematic diagram showing the DNA translocation mechanism by chromatin remodelers. The two ATPase subunit remain in "Close" state when they have high affinity for the DNA whereas, they become "Open" state when the affinity is low. The Lobe-1 and Lobe-2 subunits gain energy from ATP hydrolysis, ATP converts to ADP and Pi (Step-3) while moving about 1-2 bp to the 5′ end (Step-4).

DNA translocation by chromatin remodelers has been influenced by DNA and RNA helicase which belong to a much longer family of ATP-dependent nucleic acid translocases. The structures of monomeric DNA and RNA helicases are similar to that of three chromatin remodeler, which

are *Saccharomyces cerevisiae* Chd1, *Myceliophthora thermophila* Snf2 and ISWI (Xia *et al*., 2016).

Functions of ATP-dependent Chromatin Remodelers

The ATP-driven chromatin remodelers provide major functions associated with the nucleosomal core which is composed of histones (Fig. 3). They can act as a force to support to reposition nucleosomes which includes nucleosome assembly and organization by ejecting one of the histones, moving or repositioning the histone octamer to a different site on the DNA (Manelyte *et al*., 2013).

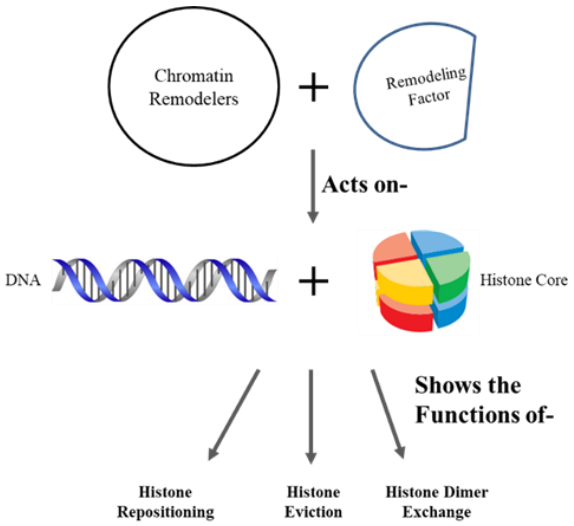

Fig. 3. Functions of ATP dependent Chromatin remodeling enzymes**.** In the presence of the chromatin remodeling factors, the remodelers act on the nucleosome that is made with DNA and histone core and exhibit multiple nucleosomal functions.

A specific family of chromatin remodeler can also render the chromatin more accessible to proteins and RNA by sliding nucleosome alongside the DNA. These enzymes act as gatekeepers and constitute a major determinant of accessory factors to nucleosome DNA, allowing a range of biological functions, including DNA damage and repair, replication, recombination and transcriptional control (Nair *et al*., 2012).

Pathophysiology and Diseases Linked with the Dysfunction of Remodelers

Chromatin remodelers ensure the dense nucleosome packaging of the DNA in a vast majority of the genome. Abnormalities of these enzymes can cause a variety of disease in human. For example, human CHD remodeler has been identified as autoantigens in patients with dermatomyositis which is a connective-tissue disease causing inflammation of both muscle and skin (Ge *et al*., 1995). Loss of ISWI can cause global transcriptional defects and can result in alteration of higher-order chromatin structure. Also, displacement of these enzymes is responsible for 20% of all cancers. The epigenetic disorder due to the misregulation of chromatin remodelers has become a major concerning factor in cancer and other neurological disorder (Mirabella *et al*., 2016). Alongside that Weaver and Sotos syndrome are some major disorders that are associated

with histone modification (Tatton-Brown *et al*., 2013). Since subunits of chromatin remodeling enzymes influence the cancer gene expression during cancer initiation, they become promising new factors for the human cancer treatment (Wang *et al*., 2007).

Conclusion

Remodelers are divided into four families based on their functions and domain organization. These chromatin remodeling complexes have direct role in gene expression either by inducing or controlling it. A significant portion of these enzyme can diffuse independently into the nucleus while acting on the nucleosomal substrates. However, the molecular mechanism still needs to be clarified at molecular level to understand and alter their functions to mitigate associated human diseases.

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