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ISWI Chromatin Remodeling Complexes: Composition and Regulation perspectives

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Abstract

In eukaryotes, chromatin plays vital role in packaging of enormous amount of genetic material into the cell nucleus. Packaging, though resolves the issue of accommodation for the genetic material, it creates the problem of accessibility for the nuclear reaction involving genetic material as template. This problem is circumvented by protein complexes that can modify and restructure chromatin *in vivo*. In the past two and half decades many protein complexes from different systems have been identified and characterized that can remodel the chromatin in ATP dependent manner. These ATP-dependent chromatin remodeling complexes collaborate in time and space with chromatin modifying enzymes and factors involved in regulation of gene expression. These multi protein complexes are essential for various cellular processes and are dynamically regulated in response to various cellular processes. Here we review compositional variation in ISWI containing remodeling complexes and their regulation by different mechanism.

Introduction

Genetic information in eukaryotes is present in the form of chromatin. Once conceived as inert packaging material for DNA into the cell, chromatin is now recognized to have diverse array of functions in genomic regulation in eukaryotes. Nucleosome is the structural unit of chromatin. It comprises an octamer of histone proteins (H3, H2A, H2B and H4) wrapped by 147 bp DNA. Nucleosome octamer in association with linker histone and non histone proteins, play important role in generation of higher order chromatin structure. Such structure of chromatin acts as general repressor for the events involving DNA as template for e.g. replication, transcription and recombination etc. The regulations of these events in context of chromatin are complex but essential event for numerous cellular processes (Roberts and Orkin 2004). Therefore an otherwise inert chromatin structure is differentially altered in time and space thus facilitating nuclear reactions like replication, transcription and recombination in response to different environmental stimulus (Becker and Hortz 2002). An environment of stearic restrictions created by chromatin is partly overcome by large multiprotein complexes that enzymatically regulate the alterations in chromatin structure. Commonly these enzyme complexes are known as chromatin remodeling complexes. These complexes are majorly categorized into two types. In first category are included those complexes that chemically modify histones

tails by acetylation, methylation, phosphorylation, ubiquitilation and/or ribosylation etc. Second category includes ATP dependent chromatin remodeling complexes that disrupt the histone DNA interactions by using energy from ATP hydrolysis (Martens and Winston 2003). Both groups of complexes may work in concerted manner or independently in time and space to modulate the accessibility of genes to sequence specific transcription factors, general transcription factors and other cellular processes requiring DNA as a template (Flaus *et al* 2006).

ATP dependent chromatin remodeling complexes are generally large multiprotein complexes containing an ATPase subunit belonging to super family II helicase-related protein. Proteins belonging to SF-II helicase contain an ATPase domain that is itself comprised of two DExx and HELICc region separated by a linker. Different types of ATP dependent chromatin remodeling complexes have been identified and isolated from models such as yeast, *Drosophila* and human. They have been classified into four families namely SWI/SNF (SWItch / Sucrose Non Fermentable) family (Cairns *et al 1994*), ISWI (Imitation SWItch) family (Ito *et al* 1997), CHD (Chromo Helicase Domain) family (Verga-Weisz *et al* 1997) and INO80 (INOsitol requiring 80) family (Shen *et al* 2000) depending on the conserved domains. Each group of remodeler has its characteristic mode of operation. Many processes in eukaryotic cells require specific type of remodeler (Clapier and Cairns 2009).

ISWI is found in many ATP dependent chromatin remodeling complexes. Its composition and function is conserved across the species (Discherl and Krebs 2004, Corona and Tamkun 2004). It is abundant and ubiquitously expressed protein in higher eukaryotes and is required for cell viability (Deuring *et al* 2000, Stopka and Skoultchi 2003). Here we present a review of different types ISWI containing complexes, their composition, function and in vivo regulation.

Types and composition

Unlike SWI/SNF, INO80 and CHD complexes that are large complexes with many subunits, ISWI complexes are comparatively small and contain only two, three or maximum four subunits. (Erdel and Rippe 2011). A novel ISWI containing complex TbISWI was also identified and purified from protozoa *Trypanosoma brucei*. It has four subunits (Stanne *et al* 2015). At least each of these complexes contains a single large subunit with many histone binding domains and an ISWI family ATPase. ISWI complexes described in mammals can be broadly classified into two categories depending upon the presence of conserved ATPase subunit either SMARKA5 (aka SNF2H) or SMARCA1 (aka SNF2L).

There are seven different ISWI complexes described in mammals, which include: NURF (one of the founding members of ISWI family), ACF, WICH, NoRC, CHRAC, RSF, and CERF (Aydin *et al* 2014). The ATPase subunit SMARCA5 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 5) is conserved in Eukaryota, while SMARCA1 (member 1) is conserved in Opisthokonta. Different complexes demonstrate compositional heterogeneity in their

subunits. These complexes are somehow capable of reading the histones and altering their affinity to underlying DNA so as to allow diverse nuclear reactions (Narlikar *et al* 2013).

NURF:

It was first discovered in *Drososphila* and demonstrates ATP dependent chromatin remodeling (Tsukiyama and Wu 1995). Mammalian NURF is a multiprotein complex containing SMARCA1, BPTF and RbAp 46/48 (Barak *et al* 2003) (Figure 1A). NURF can be considered as founding member of the ISWI family. Human and *Drosophila* NURF have been purified and demonstrated to catalyze ATP dependent nucleosome sliding activity in vitro. Human NURF is enriched in brain and regulates human *Engrailed* which is a homeo domain protein and regulates neuronal development in mid brain and hind brain (Barak *et al* 2003). The action of NURF expose or occlude transcription factor binding sites in DNA *in vivo*. Only the largest subunit NURF301 in Drosophila and BPTF in human are specific to NURF while all other subunits of NURF can form part of other remodeling complexes (Xiao *et al* 2001). Larval lethal phenotype of NURF301 suggest that it has vital transcriptional targets. NURF has also been found to physically associate with ecdysone receptors and bring about co-regulation of targets of ecdysone receptor to allow progression of larval to pupal stage (Badenhorst *et al* 2005).

CERF

In 2005 Banting *et al* reported isolation of a heterodimeric complex comprising CERC2 and SMARCA1 (Figure 1B). CERC2 is a bromodomain containing protein that recognizes acetylated lysine residues in nucleosomal histones and act as readers of epigenetic histone marks. Besides its role in ATP dependent chromatin remodeling CERC2 is also involved in integration of cytoskeletal network with processes, like vesicular trafficking, nucleocytosolic shuttling, transcription and cytokinesis. CERF complex is predominantly expressed in central nervous system. CERF demonstrates nucleosome stimulated ATP hydrolyzing activity and chromatin remodeling in vitro. It plays critical role in neurulation (Banting *et al* 2005).

ACF

Purification and characterization of an ACF (ATP utilizing chromatin assembly and Remodeling factor) from *Drosophila* was reported by J T Kadonaga group. It is composed of two subunits namely ISWI (SNF2H) and Acf1. ACF is capable of modulating inter nucleosomal spacing of chromatin in ATP dependent manner (Ito *et al* 1999). ACF catalyzes chromatin assembly as well as remodeling that occur during transcription. However ACF mediated chromatin assembly also requires histone chaperon NAP1. These observations in *Drosophila* were complimented by another study from human. ACF chromatin remodeling complex was isolated from HeLa cell by Boacher *et al* (2000). *h*ACF is considered as human counterpart of *Drosophila* ACF. In human it is composed of two subunits WCRF 135 and WRCF 180 (Figure 1C).

CHRAC:

In 1997 Beckers group identified a 670 kDa complex having five subunits from Drosophila. This complex comprises the enzyme that modulate nucleosome structure and topology of DNA in vivo (Varga Weisz *et al* 1997). CHRAC uses energy of ATP to increase accessibility of DNA to transcription factor. It can also facilitate chromatin assembly. It is now established that *Drosophila* CHARC comprises of four subunits i.e. ISWI, Acf1, CHARC 16 and CHARC 14. Whereas, its human counterpart HuCHRAC, possesses four subunits SMARCA5, hACF1, hCHRAC15 and hCHRAC17 (Figure 1D) (Poot *et al* 2000). Human CHRAC demonstrates chromatin assembly by promoting ordered spacing of nucleosome along DNA template after DNA replication. However it has also been established that nucleosome organization activities of *h*CHRAC can also promote repression of specific genes (Dirscherl and Krebs 2004)

B-WICH / WHICH,

WICH is a chromatin remodeler belonging to the ISWI family containing WSTF and SMARCA5 (Figure 1E). NM1 (Nuclear actin and Myosin 1) and WICH are associated with RNA polymerse I (Pol I) and ribosomal genes (rDNA), in which NM1 is a key regulator of gene transcription. NM1 works along with WICH to induce facilitation of transcription on chromatin. NoRC produces a repressive chromatin condensed state whereas B-WICH turns the scenario around by working alongside NM1 to activate Pol I transcription directly on chromatin template and also functions as a ribosomal chromatin structure maintenance protein (Vintermist *et al 2011*., Percipalle *et al* 2006).

Chromatin remodeling complex B-WICH is implicated in structural chromosome changes and recruits HAT (Histone acetylases) to active rRNA genes basically increasing the activity of the gene in question. Even after so much factual data available but the exact mechanism of B-WICH facilitated remodeling is unclear. However its requirement for the recruitment of HATs, PCAF, p300and GCN5, suggest that B-WICH brings about preferential access of specific factors to the DNA (Vintermist *et al*. 2011).

NoRC:

NoRC was identified as novel member of mammalian ISWI containing chromatin remodeling enzyme complex (Strohner *et al* 2001). It is composed of two subunits SMARCA5 and TIP5 (TTF 1 Interacting Protein 5) (Figure 1F). NoRC induces nucleosomes sliding in an ATP and Histone H4 tail dependant fashion. It has a special function of serving a role in the regulation of r-DNA locus. TTF-I (Transcription Termination Factor I) which acts as a multifunctional nuclear protein with NoRC, act in concert to silence rDNA transcription. The NRD (Negative regulatory domain) an N-terminal domain present in TTF-I does not allow the binding of this protein to the promoter of ribosomal genes, but the interaction of TIP5 (large subunit of NoRC) makes the TTF-I protein to interact with 160bp upstream of the

START of these ribosomal genes (Nemeth *et al* 2004, Strohner *et al 2001*). Mammmalian chromatin remodeling complexes (ChRC) can activate as well as repress transcription. NoRC basically represses the ribosomal gene expression by two mechanisms one involving TTF-I as said above and by recruiting HDAC1 (Histone deacetylase 1**).** Protein-protein interaction assay reveals association of TIP-5 the large subunit mediated deactetylation activity over rDNA promoters leading to the suppression of expression of these genes (Zhou *et al, 2002*).

ToRC: (Toutatis containg chromatin Remodeling Complex)

Emelyanov *et al* (2012) purified and characterized a conserved ISWI containing complex. It comprises of three subunits i.e ISWI, Toutatis/TIP5 and CtBP a transcriptional co repressor (Figure 1G). Toutatis [Tou] is Drosophila ortholog of TIP5 which is a large subunit of mouse NoRC. ToRC require CtBP for tethering to target sites and proper localizations. All the three subunits of ToRC are required to achieve optimal biochemical activity. However existence of complexes that possesses alternative forms of TIP5/Tou is conserved from flies to mammals. (Emelyanov *et al* 2012).

RSF

Remodeling and Spacing Factor was purified as a complex containing SMARCA5 and p325 (Rsf1) from HeLa cell lines (Figure 1H) (LeRoy *et al* 2000). It was further established that no Rsf1 (a histone chaperon) is found without SMARA5 suggesting that Rsf1 protein almost always exist as RSF in the cell. Whereas SMARCA5 can independently bind DNA, RSF complex bind DNA only in presence of histones. It has been suggested that Rsf1 modulates DNA binding activity of SMARCA5 possibly by blocking DNA binding domain of SMARCA5. Therefore both subunits are required for chromatin assembly. RSF has ATP dependant nucleosome remodeling and spacing activities (Loyola *et al* 2003). Polymerases that initiate transcription with RSF can only extend their transcription in presence of FACT (Facilitates Chromatin Transcription). This simply signals that the minimal factors required for *in vitro* transcription of chromatin template is – RSF and FACT (LeRoy *et al* 1998).

RSF forms complex with cyclin E1. This complex shows tumor promoting function in non tumorigenic cell having TP53 mutations. Over expression of Rsf-1(known as HBAXP – Hepatitis B A- antigen associated Protein) also leads to aggressive oral sqamous cell carcinoma (Fang *et al* 2011). Evidences of the RSF complex to be playing a very important role in causing DNA damage response is clear if acute expression of Rsf-1 is allowed in non-transformed cells. It causes the cells to undergo DNA strand breaks and activation of ATM pathways (Sheu *et al* 2010).

Regulation of ISWI chromatin remodeling activity

By virtue of being a multi protein assembly and broad spectrum of function demonstrated by ISWI, its chromatin remodeling activity can be influenced (or

regulated) by many factors in different cellular context in vivo. Nucleosome spacing reactions catalyzed by ISWI can be regulated (1) in *cis* by intrinsic domains of ISWI, (2) by subunits associated to ISWI, (3) by post-translational modifications of ISWI and (4) by specific DNA and RNA sequence features.

ISWI protein possesses three distinct domains. ATPase core domain is highly conserved and present in N terminal half of the ISWI protein. A characteristic set of HSS domain (HAND-SANT-SLIDE) is present in the C- terminal half of the protein (Figure 2) (Boyer *et al* 2004; Grune *et al* 2003; Hota and Bartholmew 2011). Core ATPase domain is flanked by Auto N region towards N-terminal whereas towards C-terminal it is flanked by Neg C region such that ATPase domain and HSS domains are separate by Neg C region. In between HSS domain and the C terminal end of the ISWI protein is present NLS (Nuclear localization Signal) (Figure 2) (Clapier and Cairns 2012).

Primary level of regulation in ISWI complexes occurs through structural and functional domains of ISWI protein itself. Studies from different labs have elucidated that the conserved ATPase domain has independent nucleosome remodeling activity while its adjacent domains show regulatory functions (Hota *et al* 2013; Mueller-Planitz *et al* 2013; Clapier and Cairns 2012). An ISWI protein lacking its HSS domain is capable of remodeling nucleosome and it interacts with histone H4 tail of nucleosome. It is revealed that HSS domain increases the affinity of ISWI ATPase for the nucleosome (Mueller-Planitz *et al* 2013). Yet other subunits of an ISWI complex can help in maintaining the directionality of movement of DNA into the nucleosome (Hota *et al* 2013). Auto N region acts like a brake of ISWI motor as it inhibits ATP hydrolysis by making contact with ATPase lobe. On the other hand Neg C region functions to uncouple ATPase activity from DNA translocation of the ISWI. Mutation in Atuo N and Neg C enable nucleosome sliding activity markedly insensitive to H4 basic patch, linker DNA and HSS domain (Clapier and Cairns 2012).

Nuclear import of and localization of ISWI take place by participation of nuclear localization signal in ISWI and its accessory subunits (Yadon and Tsukiyama 2011; Lan *et al* 2010; Sheu *et al* 2008). Together these findings suggest that chromatin remodeling activity is regulated by conformational changes have evolved, optimized catalysis and dynamically regulate the outcome of remodeling.

Subunits of the ISWI complex are implicated in regulation of this complex by (1) modulating nucelosome remodeling reactions and (2) targeting of ISWI containing remodeling complex to specific chromatin loci. For example; accessory subunits of human and *Drosophila* CHRAC demonstrate DNA chaperon activity (DNA binding and bending) similar to that observed in HMGB1 (Hartlepp *et al* 2005). While ISWI alone can move the nucleosome towards the end of short DNA fragment, alongwith its subunits in ACF complex it pushes the nucleosome toward the central portion of the same DNA fragment. (Eberharter *et al* 2001). Similarly ISWI subunits regulate

remodeling and nucleosome interacting ability of the complex and it localization in vivo (He *et al* 2008; Mayor *et al* 2008).

Almost all the ATP dependent chromatin remodeling complexes indentified so far demonstrate ability to recognize histone modification. It helps either in the targeting of remodeling enzyme to specific DNA region of can modulate their activity. In particular, the ISWI ATPase and its subunits show presence of dedicated domains with ability to differentiate between modified and unmodified histone tail. As mentioned above ISWI complexes require histone H4 tail for recognition and efficient remodeling. Acetylation mark on K12 and K16 on H4 tail is inhibits remodeling activity and is specifically recognized by SANT domain (Clapier *et al* 2002; Corona *et al* 2002) whereas unmodified H4 tail acts as an allosteric activator of ISWI activity (Ferreira *et al* 2007a). With the help of PHD finger domain present in some of their subunits ISWI complxes recognize and arerecruited to H3K4 methylation sites in chromatin (Wysocka *et al* 2006). Histone variants like H2A.Z generally increase the remodeling activity by ISWI (Goldman *et al* 2010). However another histone variant macroH2A negatively influence the recruitment, binding of chromatin remodeling complex (Doyen *et al* 2006). H2A.X variant bind strongly to ISWI complex and regulate DNA damage response in mammalian cell (Xiao *et al* 2009).

ISWI complexes also demonstrate their regulation through post translational modifications. It has been demonstrated that acetylation of ISWI at lysine 753 by Gcn5 is development regulated process in Drososphila (Ferreira *et al* 2007b). Poly ADP ribosylation of *d*ISWI negatively influence its ATPase and nucleosome binding activity (Arancio *et al* 2010).

Regulation of ISWI complexes by underlying DNA take place with the help of DNA binding domains present either in ATPase domain or accessory subunits of the complex. Basic feature of DNA such as bending, GC/AT content, flexibility and curvature determine its nucleosome occupancy. Nucleosome inturn influence distribution of remodeling complexes. It is now established that ISWI complexes remove nucleosome from sites of high GC content that usually favor nucleosome positioning (Moshkin *et al* 2012). ISWI complexes affinity for nucleosome and remodeling activity is strongly influenced by the length of linker DNA, structure and conformation of target DNA (Zofall *et al* 2004; Yang *et al* 2006; Rippe *et al* 2007). Targetting of NoRC to chromatin in RNA dependent manner suggests pivotal role for ncRNA in orchestrating the function of chromatin remodeling complexes (Mayer *et al* 2008).

Conclusion and future perspective:

ISWI complexes are simple in composition but dynamic in their regulation. Presences of different ISWI containing complexes are essential for life processes. Regulation of these complexes by different mechanisms in the cellular network provide window for exploring therapeutic targets in cancerous manifestations. Purification of these complexes from various other systems is awaited. Genetic and biochemical

studies from yet unexplored systems can add wealth information to the dynamic role of ISWI containing chromatin remodeling complexes.

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Figures and Legend:

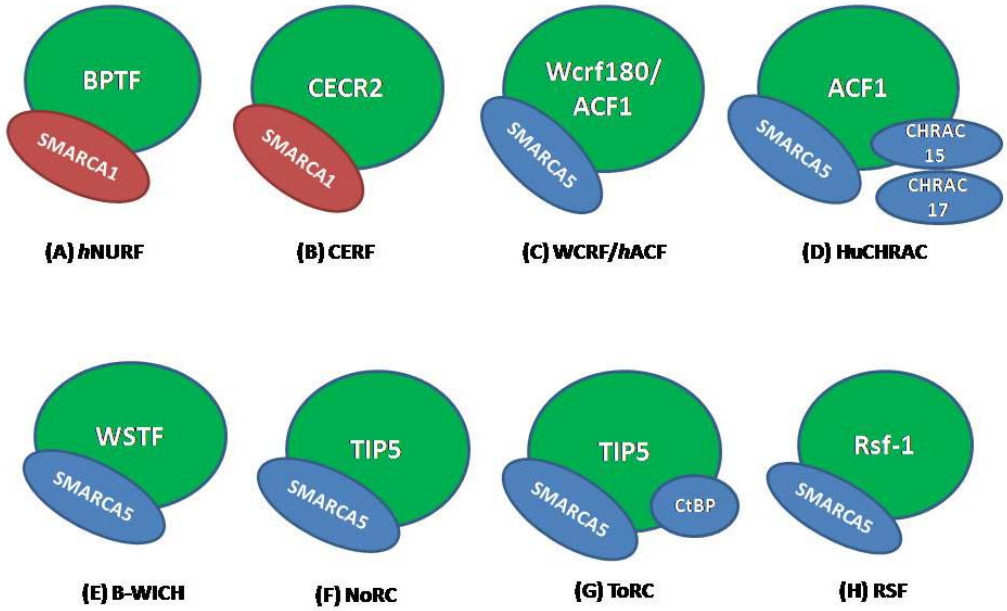

Figure 1. Mammalian ISWI complexes. There are two different classes of mammalian ISWI containing complexes i.e. those with SMARCA1 (A) hNURF and (B) CERF, and others possessing SMARCA5 (C) hACF/WCRF, (d) HuCHRAC , (E) B-WICH, (F) NoRC, (G) ToRC and (H) human RSF.

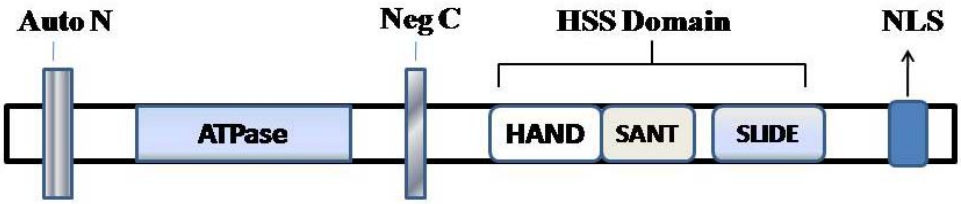

Figure 2. Structure of ISWI domains. Core ATPAse domain is flanked by Auto N region towards N terminal and NegC region towards C terminal. HSS domain (HAND-SANT-SLIDE) with DNA binding properties is present in the C terminal half of the ISWI. Toward the C terminal end of ISWI is present NLS-nuclear localization signal that helps in import and localization ISWI complxes.