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Review

The Nucleosome Remodeling Factor

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ABSTRACT

An essential component of the chromatin remodeling machinery is NURF (Nucleosome Remodeling Factor), the founding member of the ISWI family of chromatin remodeling complexes. In vertebrates and invertebrates alike, NURF has many important functions in chromatin biology including regulating transcription, establishing boundary elements, and promoting higher order chromatin structure. Since NURF is essential to many aspects of chromatin biology, knowledge of its function is required to fully understand how the genome is regulated. This review will summarize what is currently known of its biological functions, conservation in the most prominent model organisms, biochemical functions as a nucleosome remodeling enzyme, and its possible relevance to human cancer.

1. Introduction

The fundamental unit of chromatin is the nucleosome, which is composed of four basic histone proteins tightly associated with ~150 bp of DNA contained in 1.75 super helical turns [1]. In many cases, chromatin presents a significant barrier to the interaction of trans-acting factors with DNA. As such, chromatin regulates many biological processes like transcription, DNA replication, DNA repair, and DNA recombination [2]. Epigenetic mechanisms have evolved to regulate the structure of chromatin, and as a result, access to DNA. These mechanisms include the post-translational modification of histones, DNA methylation, incorporation of histone variants, and nucleosome remodeling activities [3]. Nucleosome remodeling and the incorporation of histone variants are largely accomplished through the action of ATP-dependent chromatin remodeling complexes. These complexes are a diverse family grouped into SWI/SNF, ISWI, CHD, or INO80 sub-families, based upon sequence homology of the associated ATPase [4].

Since its discovery, the ISWI family member NURF (Nucleosome Remodeling Factor) chromatin remodeling complex has been documented as a key regulator of development in many prominent model organisms. Evidence suggests that NURF is an ATP-dependent chromatin remodeling complex, specifically targeted to chromatin through interactions with sequence specific transcription factors and modified histones. To examine the evidence for this model, and come to a better understanding of NURF function, this review will: examine key points of its ATP-dependent remodeling reaction with emphasis on its interactions with the nucleosome, summarize known biological functions for NURF, identify potential NURF homologs and conserved functions by sequence conservation in major model organisms, and summarize available evidence for its role in human cancer.

2. The Nucleosome Remodeling Factor

NURF was first identified in *Drosophila melanogaster* as an ATP-dependent biochemical activity that enhanced GAGA factor (GAGAG binding factor)-mediated nuclease accessibility to reconstituted chromatin [5,6]. Biochemical purification of this activity revealed a four subunit complex composed of NURF301, the ATPase ISWI (NURF140), NURF55 and NURF38 polypeptides [7]. Purifications from human cells identified a complex highly homologous to *D. melanogaster* NURF, strongly suggesting that it has been conserved through evolution [8]. *Homo sapiens* NURF contains the NURF301 homolog BPTF, the ISWI homolog SNF2L, and a NURF55 homolog pRBAP46/48; however, a NURF38 homolog has not been identified [8] (Fig. 1A).

2.1. NURF301

D. melanogaster NURF301 has a number of functional domains found in other chromatin associated proteins (Fig. 1B). The N-terminal HMGA (High Mobility Group) domain contains two AT-hook

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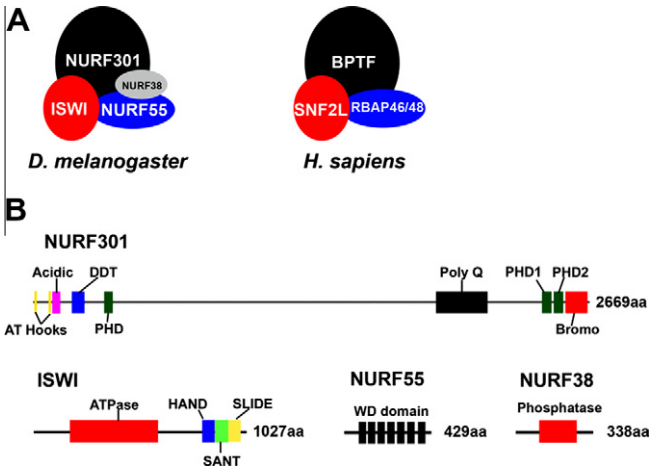

Fig. 1. Diagram of the NURF remodeling complex and its associated subunits. (A) Cartoon showing the subunit composition of *D. melanogaster* and *H. sapiens* NURF complexes. *D. melanogaster* NURF contains 4 subunits: NURF301, the largest and essential subunit; the ISWI ATPase; NURF55, a WD repeat protein; and NURF38, a pyrophosphatase. *H. sapiens* NURF has homologs strongly related to 3 of these subunits. BPTF is closely related to NURF301, SNF2L to ISWI, and pRBAP46/48 to NURF55. Interestingly, *H. sapiens* NURF does not contain a homolog of the NURF38 pyrophosphatase. (B) Domain analysis of *D. melanogaster* NURF subunits. Domains are color coded (cf. Fig. 2).

sequences and an acidic patch that interacts with nucleosomes [9]. These interactions are likely due to direct contacts with DNA because the AT hook has known affinity with the minor groove of AT rich DNA [10]. The N-terminal DDT domain (DNA-binding homeobox-containing proteins and the different transcription and chromatin remodeling factors in which they are found) and PHD finger (Plant Homeodomain Zinc Finger) have not been specifically characterized in NURF301; however, a similar DDT domain in ACF1 is essential for interactions with ISWI [11]. The NURF301 WAC and WACZ domains are not well characterized, but similar domains in ACF1 are important for its interactions with DNA [11]. The C-terminal domains include a poly-glutamate region which is intrinsically disordered, two PHD fingers, and a bromodomain [12]. The most C-terminal PHD finger (PHD2) and bromodomain compose a histone recognition module that binds di/trimethyl-K4 on histone H3 (H3K4me2/3) and acetyl-K16 on histone H4 (H4K16ac), respectively [13–15]. Additional domains include nuclear localization signals, poly-proline regions, and LXXLL motifs. The latter have been shown to be important for protein–protein interactions and could be important for interactions with nuclear hormone receptors [16].

2.2. ISWI

Characteristic regions of ISWI are the ATPase domain, common to all remodeling proteins, and the C-terminal HAND, SANT, and SLIDE domains (Fig. 1B). ATPase domains are composed of a number of highly homologous motifs (Ia, Ib, II, III, IV, V and VI) separated by less conserved spacers that vary in length between ATPase family members [17]. The ISWI ATPase domain interacts with DNA in the nucleosome, ~20 bp away from the dyad axis [18]. Similar contacts have been observed for SWI/SNF chromatin remodeling complexes, suggesting an essential function in the remodeling reaction [19]. The C-terminal HAND, SANT, and SLIDE domains are highly conserved through evolution and are diagnostic of ISWI family members. The HAND, SANT, and SLIDE domains make essential contacts with the histone H4 tail and linker DNA, and are essential to the ISWI remodeling reaction [20,21]. In addition, the ISWI ATPase contains an N-terminal AT hook, and LXXLL motifs which likely interact with the nucleosome and facilitate protein–protein interactions, respectively (see Section 2.1).

2.3. NURF55

D. melanogaster NURF55 contains the highly conserved and widely utilized WD repeat domain (Fig. 1B) [22]. WD repeat-containing proteins are present in almost all organisms and are found in many chromatin associated complexes (for example Sin3, NuRD, CAF-1, PRC2, and pRB) [23]. They are named for the presence of four or more ~40 amino acid repeating units ending with conserved Gly-His (GH) and Trp-Asp (WD) residues [24]. Interestingly, NURF301 and ISWI alone are sufficient for ATP dependent remodeling of reconstituted chromatin suggesting that NURF55 is not essential for NURF activity in vitro [9]. NURF55 is proposed to indirectly interact with chromatin in vivo, likely through chromatin associated complexes [22]. In contrast to NURF55, the *Xenopus laevis* and *H. sapiens* homologs p48 and pRBAP48, respectively, directly interact with histone H4, suggesting that they have direct interactions with chromatin [22,25,26].

2.4. NURF38

NURF38 has a strong inorganic pyrophosphatase activity (Fig. 1B) [27]. Inorganic pyrophosphatases have been highly conserved through evolution because of essential functions in phosphate and nucleotide metabolism. Interestingly, NURF38 is not required for, and functions independently of, chromatin remodeling functions. One proposed function is to hydrolyze inorganic pyrophosphates, a byproduct of the RNA polymerase reaction, to increase the efficiency of transcription [27]. Human NURF does not have an associated pyrophosphatase homolog, making its significance to NURF function unclear.

3. The NURF remodeling reaction

The minimal substrate for the NURF remodeling reaction is a nucleosome with linker DNA [6]. *D. melanogaster* NURF mobilizes nucleosomes in 10 bp bidirectional step movements between stable positioning sequences with little unwrapping of the DNA from the nucleosome surface [28,29]. This is in contrast to activities of the SWI/SNF family, which can generate large loops of DNA from the nucleosome surface and can evict histones, and the INO80 family which are dedicated histone exchange complexes [30–33]. In vitro chromatin remodeling is influenced by linker length, strength of the DNA positioning sequence for the nucleosome, and biochemical properties of the remodeling complex [34,35]. NURF slides nucleosomes into a thermodynamically stable position or to the end of a DNA fragment, rendering them refractory to further remodeling [28,29,34]. DNA binding factors and adjacent nucleosomes can strongly influence the outcome of the remodeling reaction by providing barriers to the movement of nucleosomes in cis [36]. Thus it is widely assumed that the combination of DNA binding factors, adjacent nucleosomes, and physical properties of the DNA and histones significantly contribute to the outcome of NURF remodeling reactions in vivo.

Key elements of the nucleosome are required for NURF chromatin remodeling. Nucleosomes composed of histones lacking N-terminal tails are refractory to remodeling by NURF, stressing their importance to the reaction [37]. Mutagenesis has identified the histone H4 tail and its N-terminal proximal residues 16-KRHR-19 as the most important for NURF nucleosome remodeling functions. Site directed mutation of any of these residues, or acetylation of H4K16 or H4K8 by histone acetyltransferases, significantly inhibits the ATPase activity of ISWI [9,38–41]. Acetylation at residues other