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Review

Nuclear hormone receptor co-repressors: Structure and function

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ABSTRACT

Co-repressor proteins, such as SMRT and NCoR, mediate the repressive activity of unliganded nuclear receptors and other transcription factors. They appear to act as intrinsically disordered "hub proteins" that integrate the activities of a range of transcription factors with a number of histone modifying enzymes. Although these co-repressor proteins are challenging targets for structural studies due to their largely unstructured character, a number of structures have recently been determined of co-repressor interaction regions in complex with their interacting partners. These have yielded considerable insight into the mechanism of assembly of these complexes, the structural basis for the specificity of the interactions and also open opportunities for targeting these interactions therapeutically.

Contents

1. Introduction

The regulation of gene expression by nuclear receptors plays an essential role in the regulation of growth, development and homeostasis. The nuclear receptor family comprises 48 receptors in humans, and includes receptors for which the ligand is known, adopted orphan receptors and orphan receptors for which the ligand remains as yet unknown (Mangelsdorf et al., 1995; Willson and Moore, 2002). Nuclear receptors interact with a wide family of co-regulator molecules (co-activators and co-repressors). Co-activators are generally recruited to ligand bound nuclear receptors and enhance gene expression. Co-repressors fulfill the opposite role and mainly bind to un-liganded nuclear receptors and repress transcription. Co-repressors may also play a role in "resetting" chromatin following rounds of activated transcription (Wang et al., 2009).

Two of the best studied of the nuclear receptor co-repressors are the homologous proteins SMRT and NCoR, that were first identified through their interaction with nuclear receptors in the absence of a ligand (Hörlein et al., 1995; Chen and Evans, 1995). SMRT and NCoR also interact with many other transcription factors including: BCL6, Kaiso, ETO, MEF2C, CNOT2 and CBF1 (Ahmad et al., 2003; Gelmetti et al., 1998; Jayne et al., 2006; Kao et al.,

Abbreviations: HDAC, histone deacetylase; HID, histone interaction domain; LBD, ligand binding domain; ID, interaction domain; RRM, RNA recognition motif.

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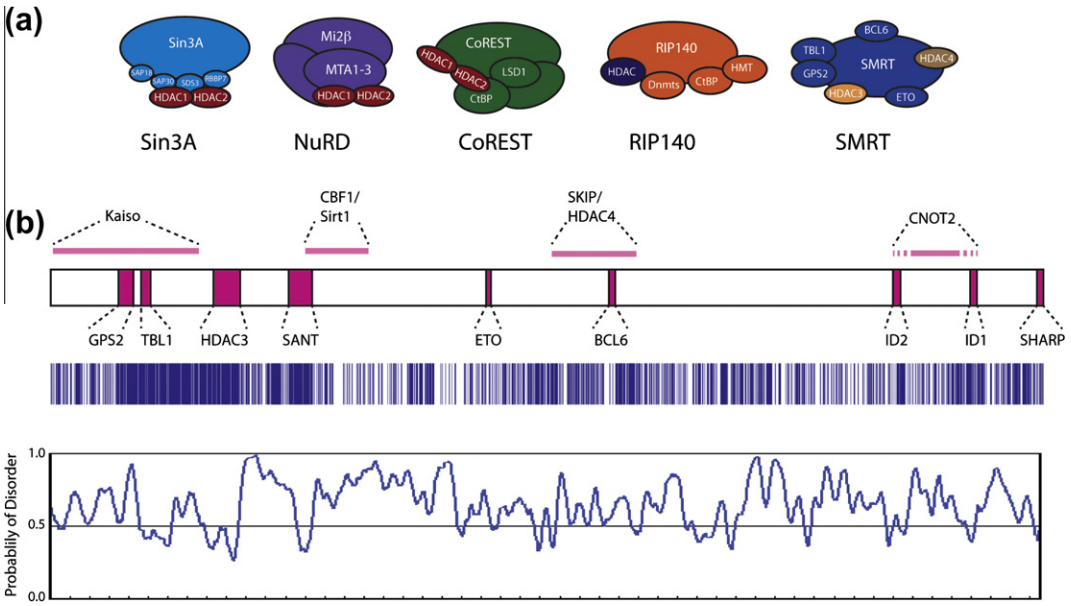

Fig. 1. The co-repressor SMRT is mostly intrinsically disordered and acts as a platform for the interaction of many proteins. (a) Schematic diagrams of histone deacetylase containing co-repressor complexes. HDAC1 and 2 are located together in three main co-repressor complexes: Sin3A, Nucleosome Remodeling and Deacetylase (NuRD) and CoREST complexes. HDAC3 exists in a stoichiometric complex with SMRT. HDAC4 also forms part of the SMRT complex. (b) Linear representation of SMRT showing the sites of interaction of various interacting partners. Interaction sites for which there is structural data available are represented by pink boxes on SMRT, interactions for which defined amino acid boundaries have been reported are indicated by solid pink boxes, interactions which are reported but no defined boundaries are available are indicated by dashed pink boxes. The sites of interaction are drawn to scale with respect to SMRT. Sequence alignment between SMRT and NCoR, blue lines show homology, the co-repression domain can be seen as the area of high homology towards the N-terminus. A disorder prediction of SMRT (generated from RONN), showing that SMRT is predicted to be mostly disordered. Increasing probability of disorder is indicated above the line, ordered regions are indicated below the line.

1998; Wu et al., 2001; Yoon et al., 2003; Lutterbach et al., 1998) (Fig. 1a). SMRT and NCoR have been purified from HeLa cell extracts by several groups and have been found to form large complexes with an apparent molecular weight of between one and two megadaltons (Guenther et al., 2000; Li et al., 2000; Wen et al., 2000). Repression is mediated by recruiting multiple histone deacetylase enzymes such as HDAC1 (Ariyoshi and Schwabe, 2003; Heinzel et al., 1997; Nagy et al., 1997), HDAC7 (Kao et al., 2000), HDAC4 (Fischle et al., 2002; Huang et al., 2000), HDAC3 (Guenther et al., 2000; Li et al., 2000) and Sirt1 (Picard et al., 2004). The relative importance of each of these enzymes has yet to be fully established; however, it has been clearly demonstrated that HDAC3 recruitment to the complex is essential for repression by the thyroid hormone receptor (Ishizuka and Lazar, 2003).

2. Overall characteristics of SMRT/NCoR

SMRT and NCoR are large, homologous proteins (ca. 2500 aa) with an overall sequence identity of 40% (Fig. 1b). Analysis of the pattern of conservation between human SMRT and NCoR shows that there are regions of high conservation separated by regions of much lower conservation. The largest region of high conservation spans a stretch of ~300 amino acids with 83% identity between the two proteins. Other regions of high conservation are smaller and generally span between 20 and 50 amino acids (Fig. 1b).

Predictions of secondary structure and of intrinsic disorder suggest that there are only a few regions that possess an intrinsically folded structure. Two of the regions that are predicted to be structured are proposed to fold into SANT-like domains (Aasland et al., 1996). The first of the SANT-like domains, whose structure is described below, has been shown to both recruit and activate HDAC3 and has been termed the deacetylase activation domain (DAD) (Codina et al., 2005; Guenther et al., 2001; Li et al., 2002; Zhang et al., 2002). The second SANT-like domain has been reported to interact directly with histone tails (the enzymatic substrate of HDAC3) and has been termed the histone interaction domain (HID) (Hartman et al., 2005; Yu et al., 2003). An overall picture is emerging in which SMRT and NCoR are largely unstructured platform proteins that act as a scaffold upon which the enzymatic machinery of the repression complex is built.

The largely intrinsically disordered nature of SMRT and NCoR, as well as other transcriptional co-regulators, seems to be a characteristic feature of these proteins and such properties are often associated with so-called hub proteins that have many interaction partners (Singh et al., 2007; Haynes et al., 2006). The characteristic of intrinsic disorder may reflect the need to make many highly specific but relatively low affinity interactions (due to the entropic cost of forming complexes).

3. Interaction of SMRT/NCoR with unliganded nuclear receptors

As mentioned earlier in Section 1, co-repressors, for the most part, interact with the ligand binding domains (LBDs) of nuclear receptors in the absence of a bound ligand. Much is known about nuclear receptor LBD structure since crystal structures of many such nuclear receptor family LBD domains have now been determined (reviewed in Jin and Yong (2010), Moras D this issue). The overall structure of the LBD is composed of a three-layer antiparallel α-helical sandwich (Fig. 2a). The central layer of helices is incomplete leaving a cavity that serves as the ligand-binding pocket. Bound ligand stabilizes the nuclear receptor conformation through direct contacts with multiple structural elements of the receptor, including helices 3, 5, 6, 7, 10, and the activation helix 12. The LBD structure forms the platform for the recruitment of both co-activator and co-repressor proteins.

In general, nuclear receptor co-activators bind to ligand bound nuclear receptors and co-repressors to un-liganded nuclear receptors (reviewed in McKenna et al. (1999) and Glass and Rosenfeld (2000)). These interactions are mediated by short receptor interac-