Nuclear receptor corepressors

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The ability of NR LBDs to transfer repression function to a heterologous DNA binding domain, and the cross-squelching of repression by untethered LBDs, has suggested that repression is mediated by interactions with putative cellular corepressor proteins. The yeast-two hybrid screen for protein interactors has proven to be the key to the isolation and characterization of corepressors. This short review will focus on N-CoR and SMRT.

Received May 3rd, 2003; Accepted June 5th, 2003; Published June 12th, 2003 | **Abbreviations:** **AML:** acute myeloid leukemia; **CoRNR box:** nuclear receptor interacting domain in corepressors; **GST:** glutathione S transferase; **H12:** helix in the ligand binding domain of many nuclear receptors |

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Background

Hormone binding to nuclear receptors has long been known to activate gene expression. In the case of steroid hormone receptors, hormone triggers dissociation from cytoplasmic chaperones, nuclear localization, and DNA binding. Hence, expression of target genes is neutral in the absence of ligand. The related thyroid hormone receptor (TR) and retinoic acid receptor (RAR) also activate gene expression in the presence of their cognate ligands but, by contrast, these receptors are constitutively nuclear and bind to DNA in the absence of ligand [Samuels et al., 1988]. Molecular analysis has revealed that the ligand binding domains (LBDs) of nuclear receptors (NRs) contain potent transcriptional repression functions [Brent et al., 1989; Graupner et al., 1989]. In addition to TR and RAR, potent repression functions have been identified in the orphan receptors liver X receptor (LXR) [Hu et al., 2003] and RevErb [Harding and Lazar, 1995].

The ability of NR LBDs to transfer repression function to a heterologous DNA binding domain, and the cross-squelching of repression by untethered LBDs, suggested that repression was mediated by interactions with putative cellular corepressor proteins [Baniahmad et al., 1995; Qi et al., 1995]. The yeast-two hybrid screen for protein interactors proved the key to the isolation and characterization of corepressors. The first corepressors identified were named N-CoR (Nuclear Receptor CoRepressor), first identified by Rosenfeld and colleagues [Horlein et al., 1995], and SMRT (Silencing Mediator of Retinoid and Thyroid Receptors, first identified by Evans and colleagues [Chen and Evans, 1995]). Other molecules that may serve as corepressors for nuclear receptors include Alien [Dressel et al., 1999], Hairless [Potter et al., 2001], LCoR [Fernandes et al., 2003], RIP-140 [Cavailles et al., 1995], and SUN-CoR [Zamir et al., 1997].

This short review will focus on N-CoR and SMRT, which have received the most attention because they are structurally related molecules that fulfill two important criteria: 1) they bind to NRs in the absence of ligand, and 2) they possess autonomous, transferable repression domains. N-CoR and SMRT are large proteins, whose NR binding and repression functions are mediated by the carboxyl and amino terminal halves of the molecules, respectively (Figure 1).

Nuclear Receptor Binding to N-CoR and SMRT

The major structural change in the NR LBD upon ligand binding is the position of helix 12 (H12), whose importance for coactivator binding has been demonstrated biochemically as well as structurally [Wurtz et al., 1996]. Intriguingly, deletion of H12 actually enhances repression and corepressor binding of several NRs, including TR [Damm et al., 1989; Sap et al., 1989], RAR [Tsai et al., 1992], RXR [Schulman et al., 1997; Zhang et al., 1999] and the orphans PPAR [Gurnell et al., 2000] and ROR [Harding et al., 1997]. Indeed, the orphan NR RevErb is a very potent repressor and does not possess H12 at all [Harding and Lazar, 1995]. The corepressors bind to a surface, composed of residues in NR helices 3, 4 and 5 that is fundamentally similar to that bound by coactivator. This was predicted from biochemical studies, which demonstrated that a "CoRNR box" motif in corepressors, similar to the "NR box" motif in coactivators [Heery et al., 1997; McInerney et al., 1998], was required for NR interaction [Hu and Lazar, 1999; Nagy et al., 1999; Perissi et al., 1999]. This has been recently proven by the first crystal structure of an NR bound to a CoRNR-box containing corepressor- derived peptide [Xu et al., 2002].

Cellular localization of N-CoR and SMRT

N-CoR and SMRT are predominantly nuclear proteins, but recent evidence suggests that changes in signaling at the cell surface can activate second messenger systems leading to protein phosphorylation and nuclear-cytoplasmic shuttling of the corepressors. In the case of SMRT, MAP kinase directed phosphorylation has been implicated [Hong et al., 2001], For N-CoR the phosphorylation of an associated protein, TAB2, by IKK kinase has been reported to induced nuclear exit [Baek et al., 2002].

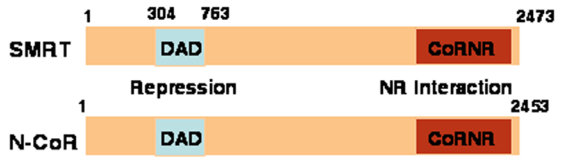

Figure 1. NR corepressors See text for details

N-CoR/SMRT-Containing Repression Complexes

A large number of proteins have been suggested to interact with N-CoR and SMRT, based upon GST-pulldown and yeast two-hybrid studies. Direct biochemical purification of the corepressors by three different groups has demonstrated a major complex involving a WD40-repeat protein called transducin α946;-like protein 1 (TBL1, or a related protein TBL1R) and histone deacetylase 3 (HDAC3) [Guenther et al., 2000; Li et al., 2000; Zhang et al., 2002]. The associated proteins are likely to mediate repression by N-CoR and SMRT, as will be discussed below. This core complex also contains G-protein suppressor 2 (GPS2) [Zhang et al., 2002] and IR-10 [Yoon et al., 2003], as well as a TBL1-related protein (Figure 2). Alternative complexes that include the HDAC1-Sin3 corepressor complex have been reported [Jones et al., 2001; Underhill et al., 2000], although studies of HDAC recruitment by NRs has implicated HDAC3 but not HDACs 1 and 2 [Ishizuka and Lazar, 2003; Li et al., 2002]. Class II HDACs have also been shown to bind strongly to N-CoR and SMRT [Huang et al., 2000; Kao et al., 2000], but their CaM-kinase dependent nuclear-cytoplasmic shuttle [Grozinger and Schreiber, 2000; McKinsey et al., 2000] may limit their interaction with NR corepressors in vivo.

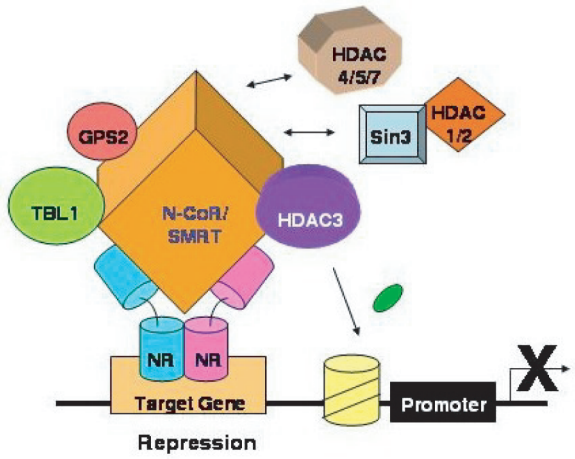

Figure 2. N-CoR/SMRT repression complexes See text for details

Mechanisms of Repression by N-CoR and SMRT

Gene expression is regulated by changes in chromatin structure that include DNA unwinding and covalent modification of nucleosomal histones [Jenuwein and Allis, 2001; Kouzarides, 2000; Schreiber and Bernstein, 2002]. SMRT and N-CoR both exist in repression complexes with HDAC enzyme activity, and HDAC3 is largely responsible for this activity [Guenther et al., 2000; Li et al., 2000; Zhang et al., 2002]. Remarkably, the enzyme activity of HDAC3 requires SMRT/N-CoR, which interacts with and activates HDAC3 via a region termed the deacetylase activation domain (DAD) [Guenther et al., 2001] . The DAD activity of NCoR and SMRT requires the N-terminal SANT1 motif [Guenther et al., 2001; Zhang et al., 2002], and the downstream SANT2 is part of a histone interaction domain that enhances this activity [Yu et al., 2003]. HDAC3 is required for repression by TR [Ishizuka and Lazar, 2003; Yoon et al., 2003], as is TBL1 which is also a histone binding protein that may function via an HDAC-independent mechanism [Guenther et al., 2000; Yoon et al., 2003].

Biological Functions of N-CoR and SMRT

There are clearly quantitative differences between N-CoR and SMRT binding to NRs both in solution, on DNA, and on target genes in living cells [Hu et al., 2001; Ishizuka and Lazar, 2003; Makowski et al., 2003; Webb et al., 2000; Zamir et al., 1997]. N-CoR and SMRT also function as corepressors for transcription factors other than NRs [Xu et al., 1998] . The best evidence that N-CoR and SMRT have non-redundant functions comes from the knockout of N-CoR, which is embryonic lethal [Jepsen et al., 2000], indicating that SMRT cannot compensate for the lack of N-CoR. NR corepressors have also been implicated in the mechanisms of human diseases, including acute promeyleocytic leukemia due to RAR translocations [Grignani et al., 1998; Guidez et al., 1998; He et al., 1998], acute myeloid leukemia due to the AML1-ETO translocation [Gelmetti et al., 1998; Lutterbach et al., 1998; Wang et al., 1998], thyroid hormone resistance [Tagami et al., 1997; Yoh et al., 1997], and insulin resistance due to mutation in PPARγ [Gurnell et al., 2000].

Future

Corepressors are complicated molecules, that mediate repression by NRs as well as other transcription factors. Their interactions with NRs are highly specific, and they repress transcription in the context of large, multiprotein complexes with several potential effectors of repression, including potent HDAC activity. These complexes are potential targets of therapy for leukemia, diabetes, and other diseases. Corepressor function may be regulated by extracellular signals, intracellular localization, and cell-specific factors, in addition to the NRs to which they bind. We are rapidly learning more about the composition and regulation of corepressor complexes, and how this regulates NR physiology and function.

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