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Coactivators and Nuclear Receptor Transactivation

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Abstract A variety of coregulator proteins serve as partners for nuclear receptors orchestrating the molecular events required for receptor-dependent transcriptional regulation. Some coregulators directly interact with nuclear receptors and provide a platform for recruitment of other factors that provide distinct biochemical activities that influence transcriptional efficiency. Coregulators can influence chromatin structure and activity via direct modification of histone proteins or by facilitating ATP-dependent chromatin remodeling. They also have the capacity to impact multiple steps in the transcription process including initiation, elongation, and mRNA splicing. Genetic analysis in humans and animal models are revealing the important cell and tissue-type specific actions of nuclear receptor coregulators as well and their role in human physiology and disease. J. Cell. Biochem. 104: 1580–1586, 2008.

Key words: nuclear receptor; coactivator; transcription; chromatin; histone

Nuclear receptors comprise a large superfamily of transcriptional regulators that mediate the cellular responses to many small signaling molecules (e.g., steroid hormones, thyroid hormone, retinoids, bile acids, fatty acids, sterols, prostaglandins, and xenobiotics). They have been instrumental in our understanding of the basic mechanisms of transcription in eukaryotes given their ability to be activated by ligand binding. This review will focus on coactivator proteins that participate directly or indirectly in the transcriptional activation activity of nuclear receptors through their diverse biochemical functions.

NUCLEAR RECEPTOR COACTIVATORS

The involvement of coregulator proteins in nuclear receptor signaling was first recognized in squelching experiments where activated receptors competed for a limited number of proteins that enhanced transcriptional activity [Meyer et al., 1989]. Nuclear receptor coactivators enhance nuclear receptor-dependent gene expression through a variety of mechanisms [Onate et al., 1995]. Most coactivator complexes are assembled onto receptor-bound promoters and stimulate transcription through direct interactions with the basal transcription machinery or by inducing histone protein modifications or local chromatin remodeling [Glass et al., 1997]. Specifically, ligand binding elicits a conformational change within helix 12 of the nuclear receptor ligand-binding domain (LBD) creating a "charge clamp" with defined residues of this helix and helix 3 that allows for interaction with LXXLL motifs of coactivators. These motifs can be divided into four different classes and are defined by the residues at positions −1 and −2 from the LXXLL motif. Furthermore, various classes of LXXLL motifs determine coactivator selectivity for nuclear receptors [Savkur and Burris, 2004].

Many coactivators possess enzymatic activities resulting in phosphorylation, acetylation, methylation, ubiquitylation, and SUMOylation of target proteins. In addition to modifying histone proteins, coactivators themselves undergo posttranslational modifications. Coregulators can be generally divided into four main groups: molecular chaperones that direct receptor maturation and trafficking (HSP90), histone modifying enzymes (e.g., histone acetyltransferases or HATs), recruiters of complexes that

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interact with the basal transcription machinery (TRAP/DRIP), and chromatin remodelers (SWI/SNF) [Chmelar et al., 2007]. Although many coactivators affect nuclear receptor-regulated transcription through their enzymatic activity, other coactivators such as hydrogen peroxide inducible clone-5 (Hic-5) and transducin β-like 1 () function as scaffold proteins, recruiting and/or stabilizing chromatin modifying coactivator complexes to target promoters [Perissi et al., 2004; Heitzer and DeFranco, 2006].

ACTION OF COACTIVATORS AT VARIOUS STEPS IN THE TRANSCRIPTIONAL ACTIVATION PROCESS

Histone Modification and Chromatin Remodeling

Of the 300 nuclear receptor coregulators that have been characterized, many possess chromatin-modifying enzymatic activity. For example, two members of the p160 family of coactivators, which includes SRC-1, transcriptional intermediary factor-2 (TIF-2/GRIP1/SRC-2), and receptor-associated coactivator-3 (RAC3/ACTR/AIB1/p/CIP/SRC-3) possess HAT activity [Glass et al., 1997]. The site-specific acetylation of histone tails induces local relaxation of chromatin, which enhances the binding of some transcriptional regulators and facilitates the recruitment and functioning of the transcriptional machinery [Jenuwein and Allis, 2001].

In addition to acetylation, histones are also modified by site-specific phosphorylation, methylation, ubiquitylation, and SUMOylation [Shilatifard, 2006]. In fact, the modification of one site often affects others, contributing to the myriad of potential modifications that comprise what is known as the "histone code" [Jenuwein and Allis, 2001]. Although alterations in chromatin structure by site-specific acetylation and phosphorylation have been described in detail, the functional role of other posttranslational modifications of histones by nuclear receptor coactivators such as coactivator associated arginine methyltransferase (CARM1) and protein arginine *N*-methyltransferase 1 (PRMT1) has yet to be fully elucidated. Both CARM1 and PRMT1 enhance nuclear receptor-mediated gene expression by methylating histone H3 and H4, respectively [Chen et al., 1999].

Chromatin Remodeling Complexes

In addition to coactivators, ATP-dependent chromatin modifying complexes such as the SWI/SNF complex are also recruited to the promoters of nuclear receptor target genes [Belandia et al., 2002]. Once these multi-subunit complexes are associated, further chromatin modifications may occur, permitting general transcription factor (GTF) recruitment [Aoyagi et al., 2005]. Some subunits within the SWI/SNF complex directly interact with nuclear receptors such as the glucocorticoid and estrogen receptors (GR and ER, respectively) [Ichinose et al., 1997; Fryer et al., 1998].

COACTIVATOR INVOLVEMENT IN THE VARIOUS STEPS DURING TRANSCRIPTION

Transcription is a multi-step process that includes chromatin remodeling, pre-initiation complex (PIC) assembly, promoter escape, elongation, and reinitiation. Although coactivators were initially characterized as proteins involved in chromatin remodeling events, recent reports indicate that they can also serve diverse roles in PIC assembly and transcriptional elongation in addition to mRNA processing.

PIC Assembly

Recent studies have shown that the multi-subunit thyroid hormone receptor associated protein (TRAP; as known as Mediator) complex not only interacts with nuclear receptors, but also members of the basal transcription machinery that constitute the PIC [Ito et al., 2002; Kang et al., 2002]. Specific subunits within the TRAP complex such as TRAP220 bind nuclear receptors while others directly interact with RNA polymerase II [Ge et al., 2002; Kang et al., 2002]. These multi-subunit complexes may serve as a bridge between promoter-specific transcriptional regulators such as nuclear receptors and their coactivators and members of the general transcription machinery.

Elongation

Recent studies have found that both some nuclear receptors as well as coregulators are involved in transcriptional elongation [Corey et al., 2003; Pascual-Le Tallec and Lombes, 2005]. For example, androgen receptor (AR) increases the efficiency of transcriptional elongation by interacting with the kinase subunit of the elongation factor, P-TEFb [Lee et al., 2001]. The principle target of P-TEFb is the carboxyl-terminal domain (CTD) of RNA polymerase II, whose hyperphosphorylation is associated with

the transition from initiation to elongation [Roeder, 1996]. Interestingly, expression of a kinase-defective P-TEFb mutant markedly reduced AR-mediated gene expression in PC3 prostate cancer cells, suggesting that AR transactivation is responsive to transcriptional elongation events. In fact, another elongation factor, Eleven-Nineteen Lysine Rich Leukemia (ELL), serves as a selective nuclear receptor coregulator [Pascual-Le Tallec and Lombes, 2005]. Specifically, ELL, a RNA polymerase II elongation factor that increases processivity by preventing polymerase pausing, interacts with mineralocorticoid receptor (MR), increasing its transcriptional activity [Shilatifard, 1998]. However, ELL inhibits GR-mediated gene expression and does not affect AR or progesterone receptor (PR)-mediated gene expression [Pascual-Le Tallec and Lombes, 2005]. Conversely, BRCA1, a subunit of the negative elongation factor (NELF) that increases RNA polymerase II pausing, interacts with ERα and represses ERα-mediated gene expression. Furthermore, members of the NELF complex are recruited to the promoters of ERα target genes in a hormone-dependent manner [Aiyar et al., 2004].

Alternative mRNA Splicing

Although the process of gene expression was once thought to occur in distinct steps that included transcription, mRNA processing, mRNA export and translation, those steps are now increasingly viewed as interrelated or coordinated events [Auboeuf et al., 2007]. How these seemingly separate events are interconnected is explained at least in part by two prevailing models. One model proposes a recruitment of splicing factors to the CTD of RNA polymerase II during transcriptional elongation while the another model links splicing to the kinetics of transcriptional elongation such that slower elongation rates would enhance mRNA splicing events [Goldstrohm et al., 2001; de la Mata et al., 2003]. Although the relationship between transcription and mRNA processing is still under investigation, what is clear is that many factors involved in transcriptional activation are also involved in mRNA processing [Auboeuf et al., 2007].

mRNA processing events are sensitive to regulators of transcription such as nuclear receptors and their coregulators. For example, ERα affects alternative mRNA splicing events of genes such as the vascular endothelial growth factor recetor-1 (VEGFR-1), reducing expression of soluble VEGFR-1 [Elkin et al., 2004]. It is thought that nuclear receptor binding to target promoters recruit coregulators that influence mRNA processing events most likely through their interaction with splicing factors or the CTD of RNA polymerase II. Nuclear receptor coregulators also affect alternative splicing of nuclear receptor target genes. Whereas the addition of steroid receptor RNA coactivator (SRA) increased exon inclusion in an ERα-regulated splicing reporter gene, the addition of coactivator activator (CoAA), a heterogeneous nuclear ribonucleoprotein-like (hnRNP) nuclear receptor coactivator, increased exon skipping [Auboeuf et al., 2007]. Furthermore, promoter-bound PGC-1, another nuclear receptor coactivator, is involved in both elongation and mRNA processing events by interacting not only with the CTD of RNA polymerase II, but also splicing factors [Monsalve et al., 2000]. Thus, in addition to being transcriptional activators that are involved in elongation events, nuclear receptor coactivators also play a crucial role in mRNA processing of nuclear receptor target genes.

DYNAMICS OF COACTIVATOR ASSEMBLY/DISASSEMBLY

Role of Chaperones

The maturation and activation of newly transformed nuclear receptors require the actions of molecular chaperones. The most notable chaperone involved with receptor regulation is heat shock protein 90 (HSP90). This regulatory protein is necessary for nuclear receptors to form complexes capable of binding ligand. Several other chaperones and co-chaperones are involved in the generation of stable nuclear receptor-HSP90 complexes in an ATP-dependent maturation process: HSP70, HSP40, Hop, and p23. Once ligand is bound to receptor complex, HSP90 allows for the interaction of co-chaperones (i.e., FKBP52, Cyp40, PP5) that aid in movement of the receptor complex to the nucleus. In addition, chaperones such as HSP90 participate in the recycling and retention of receptors within the nucleus and have been found associated with the chromatin of some nuclear receptor target genes [Pratt et al., 2004].

Receptor/Coactivator Cycles

The association of nuclear receptor coregulator complexes with DNA was once thought to be static. However, experiments utilizing chromatin immunoprecipitation (ChIP) assays and fluorescence recovery after photobleaching (FRAP) determined that receptor coregulator complex association with chromatin are dynamic [McNally et al., 2000; Shang et al., 2000]. The seminal study conducted by Shang et al. demonstrated recruitment of coactivators to hormone response elements to be cyclical in nature. Specifically, ERα was shown to bind to the Cathepsin D promoter followed by the recruitment of a variety of coactivators and then components of the transcriptional initiation apparatus. Over the course of 2 h of hormone exposure the receptor, coactivators, and transcription machinery disassemble and reassemble, prompting cycles of transcription at the promoter [Shang et al., 2000]. Results from the Gannon group suggest that there may be some order to the assembly and disassembly of distinct factors to a nuclear receptor regulated promoter [Metivier et al., 2003]. Specifically, they showed that ERα and SRC coactivators were first recruited to the pS2 promoter followed by other coactivators, Mediator, RNA polymerase II subunits and GTFs that likewise cycle in the continuous presence of hormone [Metivier et al., 2003].

Role of Proteasome and Proteasome Subunits in Nuclear Receptor Regulated Transcription

Select components of the ubiquitin-proteasome protein degradation pathway (UPP) have been identified as nuclear receptor coregulators. The influence of the UPP in nuclear receptor regulated transcription to maintain the dynamic association of receptors with chromatin at target sites extends beyond the degradation of chromatin-bound receptors and/or coregulators [Rosenfeld et al., 2006]. Monoubiquitylation of nuclear receptors and/or coregulators also regulates their transcriptional regulatory activity in the absence of degradation [Lonard and O'malley, 2007].

Phosphorylation, Ubiquitylation, and Transcriptional Time Clock

Phosphorylation is a well-recognized posttranslational modification of coregulators that modulates their activity. For example, SRC-3 has been shown to possess six distinct phosphorylation sites. Individual cellular signals lead to differential phosphorylation of SRC-3, which in turn influences its spectrum of actions in various intracellular pathways as a coactivator. Phosphorylation at all six sites is induced by estradiol and androgen, whereas TNF-α treatment only induces phosphorylation at five of the six sites. Phosphorylation defective mutants show a dramatically decreased coregulator activity, suggesting that posttranslational modification of coactivators not only delineates differential intracellular activities, but also is also necessary for their general functioning [Wu et al., 2004].

Recent work from the O'Malley group has revealed that regulation of coactivators is not limited to one type of posttranslational modification. As mentioned above, the ubiquitylation of some coactivators yields increased transcription activity. This is the case for the coactivator SRC-3 where the phosphorylated and ubiquitylated SRC-3 is more transcriptionally active than the nonubiquitylated form. Enhanced activity by ubiquitylation is dependent on an initial phosphorylation of residue S505 of SRC-3. However as expected, progressive polyubiquitylation eventually results in SRC-3 degradation. From these finding the concept of a "transcriptional time clock" arises, whereby posttranslational modifications regulate not only the activity of coactivators but also their lifetime [Wu et al., 2007].

Coactivator/Corepressor Exchange

Some unliganded nuclear receptors reside in the nucleus bound to DNA and are associated with corepressors. Corepressors nuclear receptor corepressor (NCoR) and silencing mediator of retinoic acid (SMRT) as well as many others, bind through their CoRNR-box motifs to unliganded nuclear receptors. However, upon hormone binding, conformation changes in the nuclear receptor LBD prevent corepressors from interacting and thus facilitate gene activation. Moreover, it has also been shown that dissociation of corepressors occurs through an active mechanism involving the ubiquitin-proteasome pathway. Two components of corepressor complexes, TBL1 and transducin b-like related (TBLR1) proteins, mediate the dismissal of the NCoR/SMRT holocomplex bound to repressed nuclear receptors. These two proteins serve as E3 ubiquitin ligase adaptors

for the recruitment of ubiquitylation machinery that allows for the clearing of corepressors and subsequent coactivator exchange thereby promoting gene activation [Rosenfeld et al., 2006].

COACTIVATORS AND HUMAN DISEASE

AIB1-Tamoxifen Resistant Breast Cancer

With such tightly regulated mechanisms in place to control the availability, function, and activity of coactivators within the cell, it is not surprising that much attention has been turned to investigating their potential role in pathologic processes. SRC-3 (i.e., AIB1) was the first coregulatory molecule implicated in steroid-dependent cancers, namely estrogen-sensitive breast and ovarian cancers. Interestingly, recent studies have implicated SRC-3 in tamoxifen-resistant breast cancer as well. In normal breast tissue, tamoxifen behaves as an ER antagonist through induction of a conformational change that prevents coactivator binding yet permits recruitment of corepressors [Shou et al., 2004]. However, in tissues expressing high levels of certain coactivators, such as SRC-1 or SRC-3, tamoxifen switches from an antagonist to an agonist [Shang and Brown, 2002]. ER can stimulate the growth factor receptor HER2/neu, which in turn phosphorylates SRC-3 and leads to further transcriptional activation of ER. This receptor cross talk, in the presence of elevated levels of the coactivator SRC-3, has been shown to be associated with tamoxifen resistance and worse prognosis [Shou et al., 2004].

CBP-Rubinstein/Taybe Syndrome

Rubinstein-Taybi syndrome (RSTS) is a rare disorder characterized by delayed growth and development, mental retardation, distinctive dysmorphic physical features, and an increased propensity for brain and neural crest-derived tissue tumors [Roelfsema et al., 2005]. RSTS was originally thought to result from either gross chromosomal rearrangements affecting the cAMP regulated enhancer binding protein binding protein (CBP) or point mutations in CBP, but more recent data demonstrate genetic heterogeneity with mutations in EP300, the gene encoding the coactivator p300. The closely related CBP and p300 proteins both have potent HAT activity and function as transcriptional coactivators for various nuclear receptor complexes [Kalkhoven et al., 2003]. A loss of HAT activity is responsible for the development of RSTS, and the lack of nuclear receptor specific defects may be attributed to the pleiotropic HAT activity of both CBP and p300 [Lonard et al., 2007]. RSTS serves as the first example of a defect in HAT activity leading to the development of a characterized disease.

Knockout Mouse Models

With growing evidence of the importance of coactivators in regulating nuclear receptor transcriptional activity, knockout studies have been performed to better define the function and importance of several key coactivators, namely the steroid receptor coactivator (SRC) family (Table I).

Tissue Specificity

The varying phenotypes observed in the SRC family KO mice are evidence of tissue specificity for their expression. For example, high levels of SRC-3 are expressed in oocytes, smooth muscle cells of the oviduct, vaginal epithelium, mammary gland, neurons of the hippocampus, and the olfactory bulb. Moderate expression levels were found in the smooth muscle cells of blood vessels and intestines as well as the internal granular layer of the cerebellum [Xu et al., 2000]. This differential expression can explain

TABLE I. Observed Phenotypes in SRC Knockout (KO) Mice

SRC KO	Phenotypes
SRC-1	Partial steroid and thyroid hormone resistance [Wu et al., 2004]; alterations in sexual behavior [Auger et al., 2000]; delay in cerebellar Purkinje cell development [Xu et al., 2000]; alterations in the HPA axis and generalized glucocorticoid resistance [Winnay et al., 2006]
SRC-2	Placental hypoplasia; decreased fertility in both sexes; defects in spermiogenesis and spermiation; teratozoospermia; increased lipid accumulation in Sertoli cells [Gehin et al., 2002]; resistance to obesity; greater energy production in brown adipose tissue; increased lipolysis in white adipose tissue [Xu et al., 2000]
SRC-3	Pubertal delay; decrease in female reproductive function; blunted mammary gland development; dwarfism; loss of ER-mediated vasoprotective effects following vascular trauma [Xu et al., 2000]

the observed phenotype seen in SRC-3 null mice, and also leads to additional attention to be paid to other coactivators whose expression may not be ubiquitous amongst various tissue types.

O'Malley's group found that the tissue-specific activation of the progesterone receptor (PR) is a consequence of the differential expression of SRC proteins. In SRC-1 null mice, there is a lack of PR activity following estrogen and progesterone treatment in the uterus, whereas SRC-3 null mice exhibit the expected PR activity following the same treatment. Additionally, mammary gland PR activation is seen in wild-type and SRC-1 null mice, but is absent in SRC-3 null mice. These data point to the expression of various steroid receptor coregulators as mediating the endogenous tissue-specific effects of the PR [Han et al., 2006].

In addition to tissue-specific SRC expression, other coactivators, such as Hic-5/ARA55 (Hic-5) have also been shown to be differentially expressed. Different isoforms of Hic-5 show different tissue distributions, which may explain in part the tissue specific effects of Hic-5 as well as its ability to interact with multiple nuclear receptors [Yang et al., 2000; Gao and Schwartz, 2005]. Similarly, PGC-1α has been shown to be variably expressed with highest concentrations in brown adipose tissue and cardiac muscle. PGC-1α, comparable to Hic-5, also exists in different isoforms, each of which possesses its own tissue specific distribution [Andersson and Scarpulla, 2001].

CONCLUDING REMARKS

The cell and tissue-type specificity of nuclear receptor action is dictated by their selective interactions with and recruitment of a variety of coregulators to specific gene targets. The coactivator proteins involved in nuclear receptor mediated transcriptional activation have diverse biochemical activities that relate to their participation at multiple steps in the transcriptional process. Furthermore, the regulation of coactivator expression patterns and their activity by posttranslational modifications provides additional levels of control of nuclear receptor action. The physiological impact of alterations in coregulator activity or expression makes it likely that they will be targeted for drug development to aid in the treatment of a variety of diseases.

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