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REVIEW

Sensors and signals: a coactivator/corepressor/epigenetic code for integrating signal-dependent programs of transcriptional response

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A decade of intensive investigation of coactivators and corepressors required for regulated actions of DNA-binding transcription factors has revealed a network of sequentially exchanged cofactor complexes that execute a series of enzymatic modifications required for regulated gene expression. These coregulator complexes possess “sensing” activities required for interpretation of multiple signaling pathways. In this review, we examine recent progress in understanding the functional consequences of “molecular sensor” and “molecular adaptor” actions of corepressor/coactivator complexes in integrating signal-dependent programs of transcriptional responses at the molecular level. This strategy imposes a temporal order for modifying programs of transcriptional regulation in response to the cellular milieu, which is used to mediate developmental/homeostatic and pathological events.

The physiological state of a eukaryotic cell is determined by endogenous and exogenous signals, and often the endpoint of the pathways that interpret these signals is gene transcription. In addition to regulation of the expression and activity of sequence-specific transcription factors, signaling pathways also have an impact on the epigenetic mechanisms that regulate the packaging of eukaryotic genomic DNA into a higher-ordered chromatin structure, and impart the means for memory and inheritance of information in gene promoters and their regulatory elements. Several general principles about the coactivator/corepressor network have emerged as diverse enzymatic activities in coregulator complexes have been progressively identified. First, it has become apparent

that these enzymatic activities are required not only for modification of the integral components of the coregulator complexes but also have been shown to be involved in modifications of the components of the basic transcriptional apparatus and chromatin at target gene promoters. A second principle to emerge is that many regulated transcription factors use a precise sequence of functional actions by multiple coactivator complexes for mediating gene activation. These observations raise several general questions, including: What are the biological and biochemical requirements and constraints that have driven evolution of the multitude of functionally required coactivator and corepressor complexes in metazoan organisms? What are the mechanisms that underlie the temporal order for function of the diverse enzymatic activities in coregulator complexes? How is the coregulator exchange process used to integrate dynamic changes in the signaling network and transmit these changes to the chromatin? In this review, we first present a brief overview of the functional diversity of coregulators that provide insights into the question of why so many factors have evolved to be required for transcriptional regulation. We then describe recent findings regarding the signal-dependent, cyclic turnover of transcription factors and their associated coregulator factors, and suggest ways in which these cycles are linked to epigenetic mechanisms. We conclude with examples of the ability of coactivator/corepressor complexes to serve as “sensors” that integrate signaling inputs to generate precise, complex programs of gene expression.

The coactivator/corepressor matrix

The past 10 years have permitted elucidation of a large number of complexes that have been biochemically and functionally identified to serve roles as coactivators and corepressors of specific transcriptional programs, which have been the subject of numerous comprehensive reviews (Beato et al. 1995; Mangelsdorf and Evans 1995; Willy et al. 1995; McKenna et al. 1999; Glass and Rosen-

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feld 2000; Jenuwein and Allis 2001; Rosenfeld and Glass 2001; Lin et al. 2004; Spiegelman and Heinrich 2004; Dennis and O'Malley 2005; Malik and Roeder 2005; Margueron et al. 2005; Perissi and Rosenfeld 2005). These studies have also revealed that many coactivator and corepressor proteins are components of multisubunit coregulator complexes that exhibit an ever-expanding diversity of enzymatic activities that can be divided into two generic classes (Figs. 1; 2). The first class consists of enzymes that are capable of covalently modifying histone tails such as acetylating/deacetylating activities (HATs and HDACs), methylating/demethylating enzymes (e.g., HMT and LSD1, Jamongie domain factors) (Jenuwein and Allis 2001; Bannister et al. 2002; Yoon et al. 2003b; Lee et al. 2005a; Tsukada et al. 2006), protein kinases, protein phosphatases, poly(ADP)ribosylases, ubiquitin, and SUMO ligases. The second class includes components of a family of ATP-dependent remodeling complexes (for review, see Haushalter and Kadonaga 2003; Lusser and Kadonaga 2004; Badenhorst et al. 2005; Santoso and Kadonaga 2006). Chromatin remodeling machinery, such as the SWI/SNF complex, alter the structure of the nucleosome in an ATP-dependent manner, presumably by modifying the histone-DNA interface, and often cause nucleosome sliding (Peterson 2002). The inability of the basal transcriptional machinery to effec-

tively transcribe nucleosomal DNA implies that at least one aspect of transcriptional activation involves dynamic changes in chromatin structure mandatory either for restricting or permitting binding of other transcription factors and subsequent assembly of functional pre-initiation complexes. Available evidence suggests that enzymatic activities associated with coregulator complexes are required for modifying specific components of the transcriptional apparatus and chromatin machinery in a cell-, gene-, and promoter-specific manner to enable discrete levels of combinatorial control of gene expression required for complex developmental and homeostatic programs.

While it was logical to initially consider that there might be distinct use of specific coregulator complexes by distinct classes of transcription factors or by different members of a DNA-binding transcription factor family, what has emerged is evidence of combinatorial usage. For example, many of the cofactors initially identified based on their interactions with nuclear receptors, have been found to play significant roles in mediating the actions of numerous different classes of transcription factors (for review, see Beato et al. 1995; Willy et al. 1995; Glass and Rosenfeld 2000; Rosenfeld and Glass 2001; Dennis and O'Malley 2005; Malik and Roeder 2005; Margueron et al. 2005; Perissi and Rosenfeld 2005). Con-

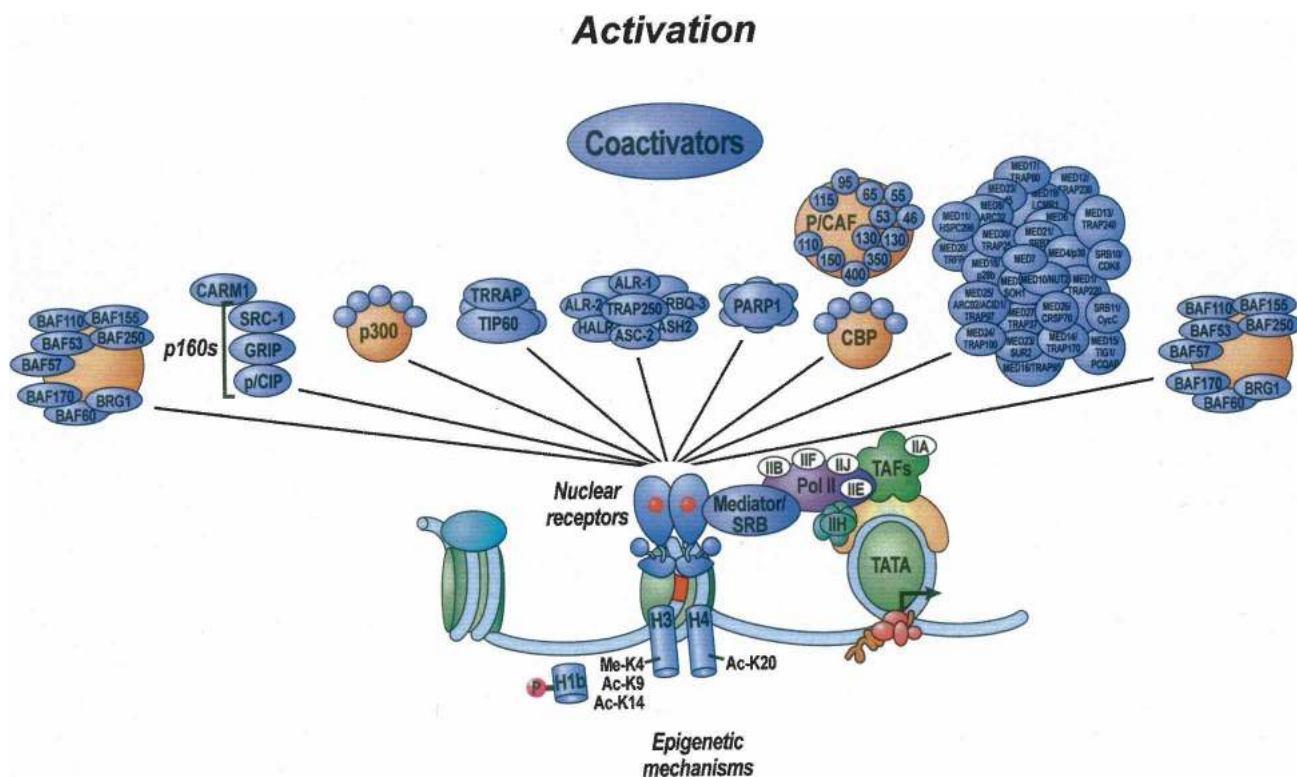


Figure 1. The coactivator matrix. Sequence-specific activators, exemplified by nuclear receptors, bind to *cis*-active elements in promoters and enhancers of target genes and activate transcription in a signal (ligand)-dependent manner. Transcriptional activation requires the actions of many, multisubunit coactivator complexes that are recruited in a parallel and/or sequential manner. Enzymatic activities associated with specific components of coactivator complexes result in nucleosome remodeling and covalent modifications of histone tails, such as histones H3K4 methylation, H3K9 and H3K9 acetylation, H4K20 acetylation, and phosphorylation of the linker histone H1b.

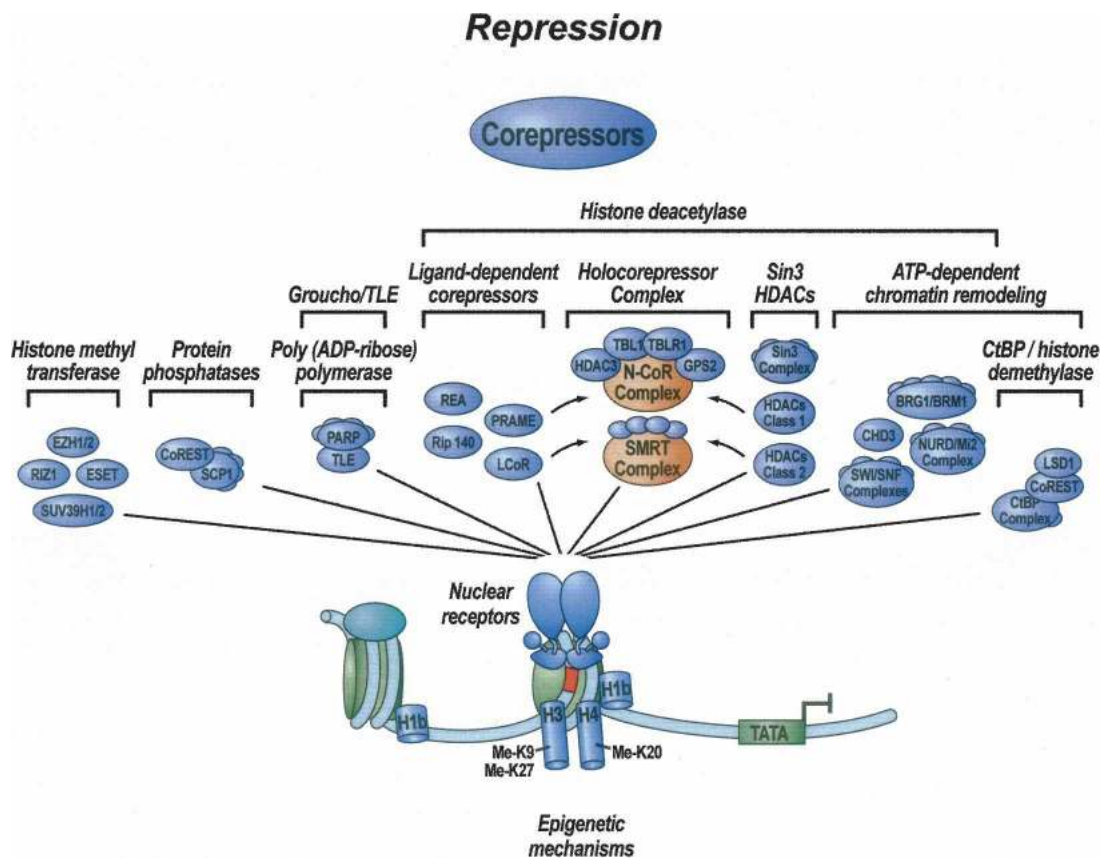


Figure 2. The corepressor matrix. Sequence-specific repressors, exemplified by unliganded or antagonist-bound nuclear receptors, actively repress transcription by recruiting corepressor complexes to *cis*-active elements in promoters and enhancers of target genes. These factors act in a combinatorial manner to antagonize actions of coactivator complexes (e.g., through histone deacetylase activity, phosphatase activity, and corepressor-associated nucleosome remodeling activities), and by mediating covalent modifications (e.g., methylation of histones H3K9, H3K27, and H4K20) that serve as marks for recruitment of additional factors involved in transcriptional repression. NCoR and SMRT nucleate a core corepressor complex that contains HDAC3, TBL1, TBLR1, and GPS2, with additional weakly interacting factors (e.g., Sin3 complexes) forming a functional holocomplex.

versely, specific transcription factors can use distinct combinations of cofactors, depending on cell type, promoter, DNA-binding site, and the actions of various signaling pathways/ligands (for review, see Willy et al. 1995; Hermanson et al. 2002). Thus, coactivator/corepressors and sequence-specific transcriptional factors constitute distinct axes on a matrix for many potential combinatorial interactions that are used in a context-dependent manner.

Dynamic exchange of enzymatic activities in coregulatory complexes

For many cofactors present in "limiting" concentrations, there is evidence that genome-wide patterns of competition for their recruitment to specific DNA-binding factors is an important quantitative determinant of overall programs of gene activation. One of the clearest examples of the "limiting" levels of a cofactor is in the Rubenstein-Tabi syndrome, in which haploinsufficiency for CBP results in severe developmental/regulatory abnormalities (Miller and Rubinstein 1995; Petrij et al.

1995; Yao et al. 1998; Oike et al. 1999a,b). An additional example supporting the concept of coactivator competition as a regulatory strategy has been provided in the Wnt pathway, where evidence from genetic screens (Das-Gupta et al. 2005) indicates that, at high levels, non-TCF/LEF factors, including homeodomain factors, can compete with TCF/LEF for nuclear β -catenin, hence dictating differential transcriptional outcome (Olson et al. 2006).

The signal-dependent interactions of coactivators and corepressors with sequence-specific transcription factors can be controlled at several levels, including cofactor expression, post-translational modifications of cofactors and their targets, and in the case of nuclear receptors, ligand binding. PPAR γ coactivator 1 α (PGC1 α) provides an instructive example. Expression of PGC1 α in brown adipose tissue is dramatically induced in response to cold exposure and β -adrenergic signaling, resulting in PGC1 α -dependent coactivation of transcriptional programs required for maintenance of core body temperature. This regulation occurs through constitutive interactions of PGC1 α with transcription factors that control

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mitochondrial biogenesis and oxidative metabolism (Puigserver and Spiegelman 2003). PGC1 α also interacts with several nuclear receptors in a ligand-dependent manner through the conserved LXXLL-containing nuclear receptor interaction domain (Heery et al. 1997; Torchia et al. 1997; Li et al. 2003; Puigserver and Spiegelman 2003). While PGC1 α coactivates many transcription factors, its ability to interact with specific factors in a constitutive or ligand-dependent manner depends on PGC1 α phosphorylation and acetylation status (Spiegelman and Heinrich 2004; Rodgers et al. 2005).

The assembly of coactivator complexes is itself a dynamic and cell-specific process, with signal transduction pathways regulating the composition of specific coactivator complex components. For example, the p160 family of coactivator proteins nucleates the assembly of multiple, distinct complexes containing diverse enzymatic activities and functions to coactivate several classes of signal-dependent transcription factors. Coactivator complex assembly is mediated by at least two interaction domains. The C-terminal domain of p160 factors mediates interactions with the histone acetyltransferases (HATs) CBP/p300 (Torchia et al. 1997), while the N-terminal basic helix-loop-helix (bHLH)/PAS domains of these factors mediate interactions with numerous additional coactivators, including coiled-coil coactivator A (CoCoA) (Kim et al. 2003), GAC63 (Chen et al. 2005), and the arginine methyltransferase CARM1 (Chen et al. 1999). These interactions are regulated by post-translational modifications that include phosphorylation, methylation, and acetylation (Lee et al. 2005c). In the case of the p160 factor SRC-3/pCIP, six phosphorylation sites have been shown to be required for coactivation of estrogen and androgen receptors, but not all of these sites are required for coactivation of NF- κ B (Wu et al. 2004). Furthermore, different combinations of site-specific phosphorylations of SRC-3 are necessary for regulation of endogenous genes involved in inflammation or transformation. Biochemical studies support the concept that modulation of SRC-3 phosphorylation alters its interactions with potential activator/coactivator partners, allowing it to function as a regulatable integrator for diverse signaling pathways. For example, phosphorylation of several residues of SRC3 is required for its effective interaction with CBP (Torchia et al. 1997; Chen et al. 1999, 2005; Kim et al. 2003; Wu et al. 2004; Lee et al. 2005c).

Structural determinants of nuclear receptors/coregulator interactions

The structural determinants of signal-dependent cofactor/transcription factor interaction have been intensively studied in the case of nuclear receptors. The nuclear receptor ligand-binding domain (LBD) consists of a three-layered, antiparallel, α -helical sandwich in which a central core layer of three helices packed between two additional layers of helices forms the ligand-binding cavity. An additional helix required for ligand-dependent

transcriptional activation (AF2) resides at the C terminus of the LBD and adopts different positions depending on the presence or absence of ligands (Bourguet et al. 1995; Renaud et al. 1995; Wagner et al. 1995; Brzozowski et al. 1997; Darimont et al. 1998; Moras and Gronemeyer 1998; Nolte et al. 1998; Shiau et al. 1998). In the presence of agonists, the activation helix is configured to form a "charge clamp" in which a conserved glutamate in the AF2 helix and a conserved lysine in helix 3 of the LBD grip the ends of helical motifs that contain an LXXLL consensus sequence present in one or more components of most coactivator complexes that are recruited to nuclear receptors (Heery et al. 1997; Torchia et al. 1997; Li et al. 2003). The leucine residues of the LXXLL helix pack into a specific hydrophobic pocket at the base of the charge clamp that stabilizes the interactions (Darimont et al. 1998; Moras and Gronemeyer 1998; Nolte et al. 1998; Shiau et al. 1998). Many coactivators contain multiple LXXLL motifs, which may be used in a nuclear receptor-specific fashion, permitting allosteric effects of differential LXXLL helix usage to modulate the efficacy of coactivator function (McInerney et al. 1998; Zhou et al. 1998; Shao et al. 2000).

Similarly, corepressors that include the nuclear receptor corepressor (NCoR) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) interact with unliganded nuclear receptors through an elongated helix of sequence LXX I/H IXXX I/L, alternatively referred to as the Cornr-box (Nagy et al. 1997; Hu and Lazar 1999; Perissi et al. 1999; Webb et al. 2000). This extended helix can occupy the same hydrophobic pocket contacted by LXXLL motifs in the absence of agonist binding due to displacement of the AF2 helix. In contrast, the extended helices of NCoR/SMRT are too long to be accommodated by this pocket when the AF2 helix assumes the charge clamp configuration in response to ligand binding. Thus, agonist binding reduces the affinity of nuclear receptors for Cornr-box-containing corepressors and increases affinity for LXXLL-containing coactivators. This conserved biochemical strategy for cofactor recruitment also allows for selection of corepressors that are recruited to nuclear receptors in a ligand-dependent manner. For example, LCoR (ligand-dependent nuclear corepressor) (Fernandes et al. 2003), RIP140 (receptor interaction protein 140) (Cavailles et al. 1995), REA (repressor of estrogen receptor activity) (Delage-Mourroux et al. 2000), and the human tumor antigen PRAME (Epping et al. 2005) are each recruited to nuclear receptors in a ligand-dependent manner via interaction with LXXLL helices, but exert corepressor functions (Fig. 2).

Covalent modifications—including phosphorylation, acetylation, sumoylation, ubiquitylation, and poly(ADP-ribosylation)—of DNA-binding factors (Rochette-Egly et al. 1997; Adam-Stitah et al. 1999; Delmotte et al. 1999; Bastien et al. 2000; Kopf et al. 2000; Gianni et al. 2002; Keriell et al. 2002) and of coactivators such as CBP are critical aspects of regulation (Yaciuk and Moran 1991; Banerjee et al. 1994; Chakravarti et al. 1999) and p300 (Janknecht and Nordheim 1996a; Chawla et al. 1998; Xu

et al. 1998; Ait-Si-Ali et al. 1999; Iwao et al. 1999; Yuan and Gambée 2000; Xu et al. 2001; Impey et al. 2002; Keriel et al. 2002; Brouillard and Cremisi 2003). For example, the nuclear factor CREB activates transcription of target genes in part through direct interactions with the KIX domain of the coactivator CBP in a phosphorylation-dependent manner (Radhakrishnan et al. 1997; Impey and Goodman 2001; Mayr et al. 2001). The complex formed by the phosphorylated kinase-inducible domain (pKID) of CREB with KIX reveals that pKID undergoes a coil-to-helix folding transition upon binding to KIX, forming two α -helices. One helix of pKID is amphipathic and interacts with a hydrophobic groove defined by helices $\alpha 1$ and $\alpha 3$ of KIX, while the second pKID helix contacts a different face of the $\alpha 3$ helix. The critical phosphate group of pKID forms a hydrogen bond to the side chain of Tyr 658 of KIX, providing a model for phosphorylation-dependent interactions between other transactivation domains and their targets. An arginine methyltransferase, CARM1, can methylate residues in the KIX domain of CBP that inhibit CREB interactions, with resultant CBP redistribution (Xu et al. 2001). Similarly, corepressors, including NCoR/SMRT, are modulated by phosphorylation (Hong and Privalsky 2000; Zhou et al. 2001; Baek et al. 2002; Hermanson et al. 2002), ubiquitylation, and sumoylation events (Hong and Privalsky 2000; Zhou et al. 2001; Baek et al. 2002; Hermanson et al. 2002; Jonas and Privalsky 2004). For example, IKK α phosphorylates SMRT, permitting ubiquitylation and export from the nucleus, and this appears to occur in a cycling mode (Hoberg et al. 2004). In parallel, IKK α can cause S10-H3 phosphorylation and also controls acetylation of K14-H3, thus implying the specialized function of the inflammatory cytokines in regulation of specific depression pathways (Anest et al. 2003; Yamamoto et al. 2003).

Allosteric effect of DNA-binding site dictates coregulator interactions outcome

An important, but poorly understood, determinant of coregulator interaction is the allosteric influence of specific DNA-binding sites on the utilization of activation and repression domains by sequence-specific DNA-binding factors. For some nuclear receptors, the specific spacing and orientation of core binding sites can be responsible for determining positive or negative gene regulation in response to ligand. In the case of retinoic acid receptor (RAR)/retinoid X receptor (RXR) heterodimers, positive or negative regulation has been shown to be strongly influenced by the spacing of direct repeat elements to which they bind (Kurokawa et al. 1994). The ability of the glucocorticoid receptor to positively or negatively regulate the proliferin gene was similarly linked to the specific sequence of a composite glucocorticoid receptor/AP-1-binding site and the presence or absence of c-Jun/c-Fos (Diamond et al. 1990). Pit1, a POU domain factor with a bipartite DNA-binding domain, proved to be differentially configured on distinct gene-specific DNA-

binding sites, leading to alternative roles as a transcriptional activator or repressor (Scully et al. 2000).

Recent studies suggest that DNA site-specific effects on transcription factor activity are linked to site-specific interactions with corepressors or coactivators. Binding sites that mediate ligand-dependent negative gene regulation by estrogen receptor α (ER α) appear to be different from conventional EREs that mediate positive transcriptional responses, and enable ER α to recruit NCoR corepressor complexes through a conserved N-terminal domain (Zhu et al. 2006). Similarly a single base pair alteration in the NF- κ B DNA-binding site causes distinct coactivator selection, providing a molecular mechanism by which distinct cohorts of target genes are activated by different inflammatory signals (Leung et al. 2004). The structural basis for allosteric regulation of transcription factor function and alternative coregulator interaction remains an important, largely unsolved problem in regulated gene expression.

Signal-dependent activator/coactivator cycles and epigenetic control

The initially defined example of signal-dependent, temporal-specific factor exchange was provided by study of the HO locus in budding yeast, with ordered recruitment of SWI5 and SBF, the SWI/SNF complex, the SAGA complex, and finally the Ash1 repressor (Cosma 2002). This ordered exchange not only defines the sequence in recruitment of enzymatic machinery necessary to achieve activation of specific transcription units, but also provides a temporally changing complement of potential "sensors" for responding to changes in the signaling milieu of the cells, and hence the opportunity to modify the transcriptional outcome. Increasing evidence indicates that active exchange cycles of sequence-specific transcription factors and associated coregulators are required for sustained transcriptional responses to signaling inputs in metazoan organisms. In this section, we review mechanisms mediating turnover of transcription factors and discuss recent findings that relate temporal cycles of transcription factor/coactivator exchange to epigenetic mechanisms that underlie regulated gene expression.

Ubiquitination as a signal for transcriptional dynamic

Signal-dependent turnover has been correlated with transcriptional activation for several members of the nuclear receptor superfamily. In the case of the ER α , for example, proteasome-mediated degradation and estrogen-dependent transactivation are inherently linked, acting to continuously turn over the estrogen receptor on active promoters. This linkage provides one level of a molecular sensor mechanism, in that each cycle of receptor turnover serves to reassess the concentration of hormone (Welshons et al. 1993; El Khissi and Leclercq 1999; Nawaz et al. 1999; Reid et al. 2003). Findings consistent with these have been reported in the case of thyroid receptors (Dace et al. 2000), retinoic acid receptors (Kopf et

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al. 2000), progesterone receptors (Lange et al. 2000), PPAR α (Blanquart et al. 2002), PPAR γ (Hauser et al. 2000), vitamin D receptor (Masuyama and MacDonald 1998; Li et al. 1999), and androgen receptor (Sheflin et al. 2000). This implies the significance of 26S proteasome functions in temporal events underlying transcription initiation. In this regard, the formation of the polyubiquitin chains by generating isopeptide bonds between K48 and G76 of ubiquitin is generally correlated with recruitment and action by the 26S proteasome. Other classes of DNA-binding transcription factors, such as NF- κ B, also exhibit similar dynamics, consistent with the model that cyclic recruitment/dismissal of transcription factors is a common feature of regulated gene expression and serves as a molecular sensing system for temporal changes in signaling inputs (Tanaka and Ichihara 1990; Baumeister et al. 1998; Hofmann and Pickart 1999; Ishizuka et al. 2001; Auboeuf et al. 2004).

These ubiquitylation/proteasome strategies also appear to function as components of the turnover of many complexes, although it is now reported that some coactivators such as A1B1/p/CIP/TRAM1/ACTR/RAC3, SRC3 can be targeted for degradation in a ubiquitylation and ATP-independent manner (Morris et al. 2003; Gillette et al. 2004; Li et al. 2006). In addition, while the recruitment of the ubiquitylation/19S proteasome for dismissal of DNA-binding transcription factors or/and coactivators/corepressors appears to be a commonly used mechanism, it is not universally required for transcription factor function. In the case of the glucocorticoid receptor (GR), blocking of the 26S proteasome with MG132 increased glucocorticoid receptor promoter binding. Similarly, inhibition of proteasome function correlates with enhanced transcriptional activation of the androgen receptor (Lin et al. 2002a,b). Nevertheless, studies of the glucocorticoid receptor and progesterone receptor occupancy on an integrated MMTV promoter in live cells indicate a very rapid rate of exchange in the presence of agonists (McNally et al. 2000; Rayasam et al. 2005). In vitro studies of glucocorticoid receptor binding to the chromatinized MMTV promoter indicate that the hSWI/SNF chromatin remodeling complex mediates its active displacement in an ATP-dependent manner (Nagaich et al. 2004), illustrating an alternative strategy for activator turnover. Intriguingly, in a cell model using multiple repeat copies of the MMTV promoter, and using photobleaching microscopy, removal of GR and PR and cofactors occurs with a periodicity of seconds (McNally et al. 2000; Nagaich et al. 2004). These results may reflect an aspect of factor release distinct from the larger cycles of dismissal revealed by chromatin immunoprecipitation (ChIP) analysis. Of particular interest would be a similar photobleaching analysis for other nuclear receptors, such as SCR and AR.

Cycling model of nuclear receptor/coregulators recruitment and transcriptional control

Evaluation of the kinetics of promoter occupancy by nuclear receptors and NF- κ B factors has revealed that, for

at least some target genes, there was a cyclical pattern of factor recruitment and dismissal in the presence of a constant activating stimulus. In the case of ER α binding to the *pS2* promoter following addition of estradiol, for example, ER α turnover was observed with a cycle time of ~40 min (Metivier et al. 2003). Furthermore, recycling of liganded ER α on the *pS2* promoter was dependent on proteasome activity (Reid et al. 2003). In a similar fashion, there was a specific order of engagement/dismissal of the order p160 factors, HATS, TAFs, Mediator, ASC2, PARP1, Mediator, Pol II, chromatin remodeling complexes; and methyltransferases, Mi2/HDACs/NCoR, and elongation complexes have been identified (Metivier et al. 2003). Similar events are recorded on many regulated transcription units (Shang et al. 2000; Baek et al. 2002; Cosma 2002; Kioussi et al. 2002; Metivier et al. 2003; Reid et al. 2003; An et al. 2004).

A general model for a periodic cycle of estrogen receptor/coregulator recruitment is presented in Figure 3. In this model, SWI/SNF complexes are recruited during both the transcription factor clearance phase, in association with recruitment of HDAC, NCoR, and NURD complexes and during the stage of sequential exchange of coactivators (Metivier et al. 2003). Intriguingly, even in the absence of ligands, many or most nuclear receptors can bind and, under certain conditions, activate these transcription events on the basal level. Similar events occur for other regulated transcription units. These findings suggest that a specific order of histone/factor modifications permits the alteration in chromatin structure that underlies transcriptional activation.

Acetylation as a dynamic signal for transcriptional response

This ordered pattern of recruitment of distinct cohorts of coregulatory complexes and their exchange indicates the need for complementary recruitment and/or actions of histone/factor-modifying enzymes. Modulatory roles of covalent modifications dictate inclusion or exclusion of specific interactive subunits from complexes, which could affect dose-response curves (Wang et al. 2004), or even a switch of activator/repressor function, based on covalent modulation of protein-protein interacting/enzymatic domains, exemplified in the case of CBP/p300 (Berger 1999; Senger et al. 2000; Huang et al. 2003). For example, the enhanceosome that regulates the *interferon* β gene is assembled in a nucleosome-free enhancer region, and it activates transcription by instructing a recruitment program of chromatin-modifying activities that target a strategically positioned nucleosome masking the TATA-box and start site of transcription (Kim et al. 1998; Munshi et al. 1998; Yie et al. 1999; Agalioti et al. 2000). In this case, recruitment of the GCN5/p/CAF complex, which acetylates the nucleosome, is followed by recruitment of the CBP-Pol II holoenzyme complex (Merika et al. 1998; Yie et al. 1999). Nucleosome acetylation, in turn, facilitates SWI/SNF recruitment by CBP, resulting in chromatin remodeling and binding of TFIID to the promoter (Agalioti et al. 2000; Munshi et al. 2001).

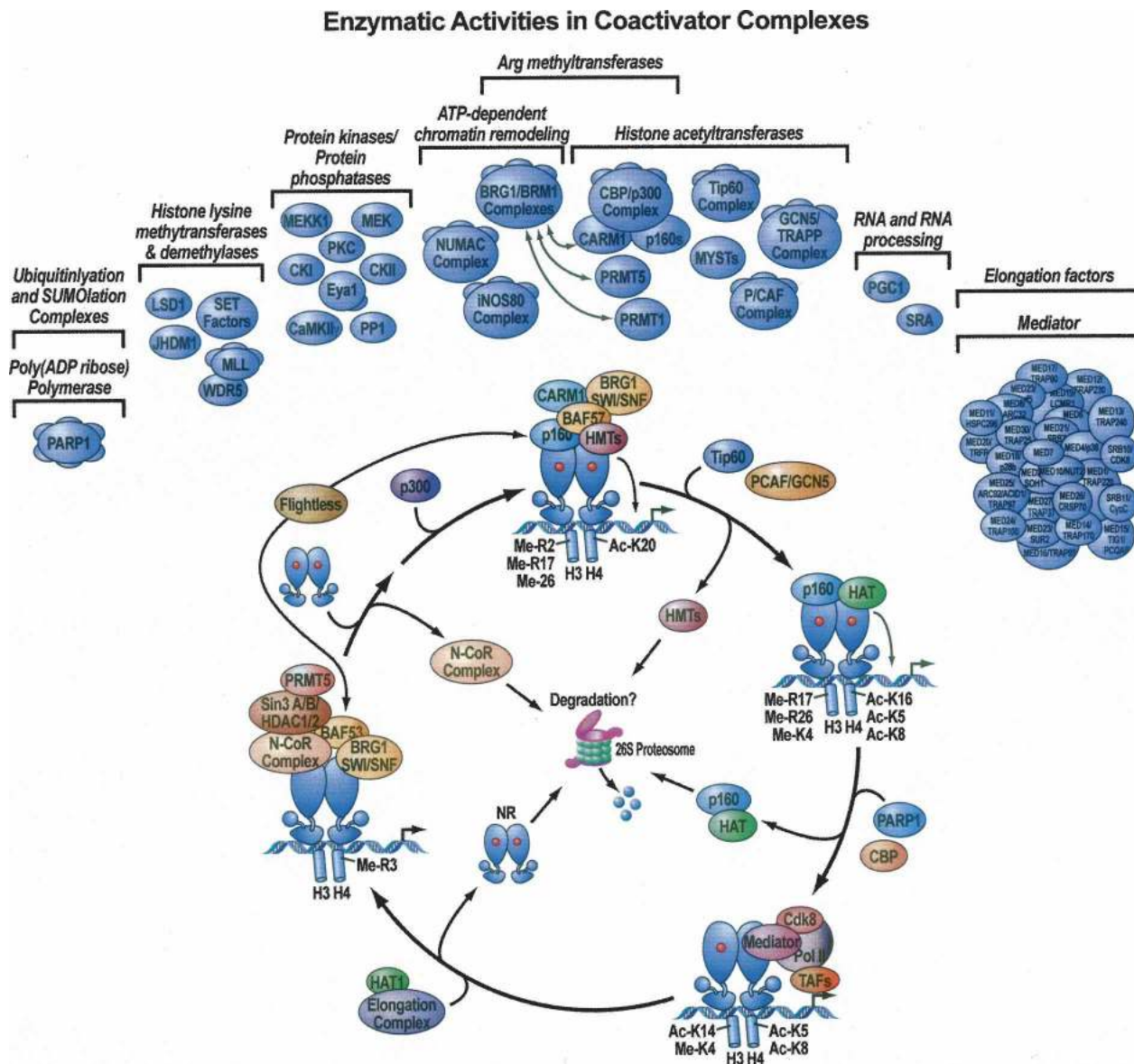


Figure 3. Linking the coregulator exchange cycle to epigenetic modifications. Estrogen-dependent activation of the pS2 gene is associated with cyclical recruitment and dismissal of the estrogen receptor, in concert with a cyclical exchange of corepressors and coactivators, providing a molecular sensing mechanism for temporal changes in signaling inputs. In the *top* panel, many of the coregulatory complexes implicated in ER α activation are illustrated in conjunction with their associated enzymatic activities (Mettivier et al. 2003). In the *bottom* panel, a temporal order of exchange is suggested, in which NCoR corepressor complexes are dismissed upon estrogen binding. p300, p160 factors, and histone arginine and lysine methyltransferases are recruited in the next phases of the cycle.

Similarly, acetylation is mediated by a series of HATs that exhibit an overlapping, but clearly distinct pattern of histone modifications and that also exhibit distinct roles on other components of regulated and core transcriptional machinery. HAT families include the CBP/p300 family, the GCN5-related HATs (GCN5L/p/CAF), the MYST family members (MOZ, NMORF/HBO1, Tip60) (for review, see Carrozza et al. 2003), and TAF250 (Neuwald and Landsman 1997; Roth et al. 2001), and their orchestrated action in conjunction with temporal order of transcription initiation events probably depends

on specialized protein domains capable of interaction with diverse chromatin modifications.

MYST HATs modify histones H2A, H3, and H4 (Clarke et al. 1999; Roth et al. 2001), with histones H4 and H2A preferred as nucleosomal substrates (Grant et al. 1997; Allard et al. 1999; Ikura et al. 2000). For example, Tip60 protein is a component of many complexes, including the TRRAP complex (Vassilev et al. 1998; Ikura et al. 2000; Pray-Grant et al. 2002). A unique feature of the Tip60 complex, compared with other MYST family members, is the presence of Ruv1/Ruv2

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(Reptin/Pontin), ATP-dependent DNA helicases, which suggest the simultaneous actions of these two enzymatic activities in the cofactor exchange cycle. Indeed, analysis of recycling events on the *pS2* promoter suggests an ordered recruitment of p300, Tip60, GCN5, p/CAF, CBP, and TAF p250, possibly in concert with acetylation of K16-H4, followed by K14-H3 (Metivier et al. 2003). The distinct chromatin-modifying actions of each enzyme and differences in timing are consistent with the selective substrates for Tip60 (H2A and H4) and p/CAF (H3/H4) (Figs. 3, 4). As Tip60 is linked to both DNA damage/repair and transcriptional activation events, the MYST complexes have components that can serve as sensors for both DNA damage and for gene transcription. These specific modifications are consistent with the well-studied yeast HAT/GCN5, a component of the SAGA/ADA complex, or the HAT-A2 complex, which acetylates histones (Grant et al. 1997; Sendra et al. 2000), including histones H3 and H4. Here, recruitment of SAGA is associated with K9/14/18/23 acetylation of histone H3, while the ADA complex is associated with K9/14/18 acetylation of histone H4 (Workman and Kingston 1998).

Some of the cofactors are mutually “corecruited,” as assessed by two-step ChIP analysis—such as Tip60 with p/CIP/AIB1—while recruitment of others coincide, for example, SRC1 with p/CIF/A1B1, CBP with Tip60, or CARM1 with PRMT1 (Metivier et al. 2003; Baek et al. 2006). Similar events can be observed during transcriptional activation by other classes of DNA-binding transcription factors, but whether the precise order for factor/histone modifications is observed is not yet clearly established. It remains to be established whether this order of recruitment and the enzymatic components of the complexes for a specific transcription factor are distinct for different cohorts of regulated genes, because the allosteric effects of DNA-binding sites would suggest that these are clear distinctions. Several examples include the exclusion or inclusion of specific cofactors dependent on the ligand used for activation of nuclear receptors including PPAR γ or AR (Picard et al. 2002; Baek et al. 2006; Wang et al. 2006). However, it is also likely that certain DNA-binding transcription factors use distinct machinery, best exemplified by studies of the Notch/Delta pathway or p50 homeodomain-dependent activation (for review, see Fryer et al. 2004).

Chromatin modifications as signals for dynamic transcriptional modulation

In recent years, more unified and consolidated molecular models have emerged to give better insights into the roles and dynamics of coregulator exchange and their interplay with functional consequences of histone modification. Although the information about a wide variety of histone modifications is accumulating at a rapid rate, the relationship between the regulated transcriptional cycle and different modifications and their composite readout is not yet clear. Clearly, this is an interdependent cycle, where histone-modifying enzymes are unable to assess their substrates unless they are targeted, and

	Site	Mod Enz	Bnd Fx	Effect	
H1b	Me-K26	EZH2	-		
	Ac-K26	-	-		
	P-S3	PP1	-	Activation	
H2A	Me-K95	-	-		
	Me-K99	-	-		
	Ac-K5	Tip60	-	Activation	
	Ac-K9	CBP/p300?	-	Activation	
	Ac-K13	CBP/p300?	-	Activation	
	P-S1	-	-		
	P-T120	-	-		
Ub-K119	Ring1B	-	Repression		
H2B	Ac-K5	Tip60	-	Activation	
	P-S14	MST1 kinase	-		
	Ub-K120	Rad6/Bre1	Rpt4/Rpt6 (19S proteasome)	→ Me-K4H3 → Me-K89H3 → Me-K36H3	
	deUb-K120	UPC8	pSET		
H2AX	P-S139	ATR/DNA-PK	Nhp10/cohesin	→ Ac-K8H4	
H3	Me-R2	CARM1	-	Activation	
	Me-R8	PRMT5	-	Repression	
	Me-R17	CARM1 PADI4	-	Activation	
	Me-R26	CARM1 PADI4	-	Activation	
	Me-K4	SET1/MLL/ MLL2/MLL3/ Ash1/SMYD3 LSD1	Chd1/WDR5/ SNF2M(blocks NURD)/ ISWI(promotes recruitment of RRA15)	→ Me-K9H3 → Ac-K9/K14/K17/K23H3 → Ac-K5/K8/K12/K16H4	
	Me-K9	SUV39H1/G9A/ EuHMase/ ESET/RIZ1/Ash1	Mp1 α /Mp1 β (CBX family)	→ Me-K20H4 → Me-K4H3 → Ac-K9/K17/K23H3	
	Me-K27	EZH2/EED/ YYAZ1	PC (Polycomb)/ Ring1a/b (E3 ligase)	→ Ub of H2A/K26H3 Repression	
	Me-K36	NSD1/SET2	JHD1		
	Me-K79	DOT1(L)	53Bp1 p53 binding protein (TAFII250)	Activation	
	Ac-K9	(GCN/PCAF/ TAFII250)	(TAFII250)		
	Ac-K14	MOF/MORF/ MOZ/Tip60/ GCN/PCAF	(TAFII250)	→ Me-K20H4	
	P-S10	Aurora B	-	→ Ac-K9H3/Ac-K20H4 → Ac-K9/K14H3	
	H4	Me-R3	PRMT1/PRMT5	-	→ Ac-K5/K8H4
		Me-K20	NSD1/PR/SET7/ SUV4-20H1/SET8/ SUV4-20H2/Ash1	Ceb2	→ Ac-K16H4 Repression
Me-K59		-	-		
Ac-K5		HAT-B/GCN/PCAF/p300	-	Activation	
Ac-K8		GCN/PCAF/p300	Brg1	→ Me-R3H4	
Ac-K12		HAT-B	-	Activation	
Ac-K16		-	-	→ Me-K20H4	
Ac-K20		-	-	Activation	

Figure 4. Coactivators and histone modifications. Many of the residues that are potentially capable of being enzymatically modified are illustrated, along with the known corresponding factor(s), its binding partner, and the effect of the modification on transcription-positive or negative → positive response - negative response (Sarnow et al. 1981; Chang et al. 1997; Davie et al. 1999; Hsu et al. 2000; Rea et al. 2000; Bannister et al. 2001; Briggs et al. 2001; Burma et al. 2001; Chadee et al. 2002; Dover et al. 2002; Fang et al. 2002; Ng et al. 2002; Nishioka et al. 2002; Schultz et al. 2002; Strahl et al. 2002; Sun and Allis 2002; Tachibana et al. 2002; Henry et al. 2003; Hwang et al. 2003; Lehnertz et al. 2003; Peters et al. 2003; Rice et al. 2003; Wood et al. 2003; Daniel et al. 2004; Ezhkova and Tansey 2004; Kuzmichev et al. 2004; Reinberg et al. 2004; Stiff et al. 2004; Karachentsev et al. 2005; Margueron et al. 2005; Wang et al. 2005).

the same enzyme will not modify all histones in all genes at the same time. The fine-tuning of the temporal order of coactivator recruitment dictated by combinations of promoter-specific transcriptional factors is central to their actions as periodic molecular sensors of a constantly diverging signaling network. Within this context, protein domains in these factors are able to recog-

nize specific modifications, including bromodomain, chromodomains, RING fingers, Ph.D. fingers, F-boxes, and SANT domains; and recognition sequences for SUMO ligases, protein kinases, and protein phosphatases play critical roles in the targeting process (Fig. 4). Each of these protein modules can contribute to both the recognition of specific histone modifications as well as to their settings at given locations. An example is provided by the identification of a WD-40 domain protein, WDR5, as a factor that recruits a complex containing methyltransferases to diMe K4-H3 (Dou et al. 2005; Wysocka et al. 2005). It has been proposed that chromatin-binding domains could play a central role in helping to establish and maintain either periodicity in transcriptional states or long-term transcriptional states when it is needed. For example, the bromodomain of BRG1 binds the H4 tail when acetylated at K8 (Agalioti et al. 2002), and the double bromodomain of TAFII250 binds the H3 tail acetylated at both K9 and K14 (Jacobson et al. 2000). These dynamic, "histone code"-driven interactions can represent the sequential order of step-to-step transitions during transcriptional initiation.

Interestingly, while p300 and p/CAT/GCN5L harbor bromodomains, CBP uniquely requires a Ph.D. finger for HAT function. In contrast, Tip60 and MOF have chromodomains, but no bromo- or Ph.D. finger domain. The presence of these domains in different HATS is consistent with the specific, preferred timing for their recruitment in the "activation cycle," in accord with the suggestion that the coactivators appear serially (Figs. 3, 4).

With respect to repression, the chromodomain of HP1 recognizes methylated K9 of H3 to provide long-term transcriptional silencing (Richards and Elgin 2002; Volpe et al. 2002). A SET domain factor, RD1/BF1/Blimp1, recruits an H3-K9 methyltransferase as a component of transcriptional silencing (Angelin-Duclos et al. 2002; Dennis and O'Malley 2005; Johnson et al. 2005). Moreover, recent studies demonstrate that some chromatin-binding factors can change the substrate specificity of chromatin-modifying enzymes, exemplified by recruitment of LSD1 to targeted promoters through COREST, where diMe K4-H3 is a preferred substrate for demethylase (Shi et al. 2004, 2005; Lee et al. 2005b). In contrast, when LSD1 is recruited via the androgen receptor, it functions as a K9-H3 demethylase and acts to stimulate ligand-dependent transcription (Metzger et al. 2005). The existence of many methylated histone residues implies the existence of many demethylases, and the discovery of the JHDM1 as a histone K36-H3 demethylase suggests that the large family of JmjC-domain-containing proteins is likely to account for many of these activities (Tsukada et al. 2006).

The existence of a specific order of the actions of the histone/factor-modifying complexes implies a signaling pathway for mediating gene activation/repression events, and for temporal-specific "sensors" responding to additional signaling pathways activated/extinguished during the periodic time intervals of coregulator exchange. These events would seem to depend on a "feed forward" system, by which marks that cause a preferen-

tial recruitment of one complex must be altered to permit sequential recruitment of the next complex in the cascade, causing the alterations in promoter complex and histone marks that elicit the next cohort of cofactor recruitment. This exchange also requires a strategy for rapid cofactor complex clearance, and probably for their degradation and/or relocation. The implication of these events is that a constantly changing array of histone modifications and coactivator complexes combinatorially serves as the platform for recruitment of the next cofactor complex, based on actions of each preceding complex. These would involve changes in the DNA-binding factor/histone modifications, changes in factor/core machinery, and altered enzymatic actions, as well as allosteric effects of DNA-binding sites, that together dictate the choice of the next group of cofactor complexes. This cycle of recruitment of specific modifying complexes in response to covalent modifications of histones is consistent with current views of the "histone code" (Jenuwein and Allis 2001; Fischle et al. 2003) as a three-dimensional platform for recruitment of coregulatory complexes. Potential relationships between histone marks and factor/cofactor recruitment can actually impose regulatory constraints on transcription factors that might otherwise function as constitutive activators or repressors (Figs. 3, 4). The actions of three-dimensional histone/factor recruitment platforms imply that multiple recognition motifs combinatorially modulate cofactor/enzyme complex recruitment events.

Gene activation and corepressor/coactivator exchange

For many genes, a key step in signal-dependent transcriptional regulation is the highly modulated switch from gene repression to gene activation, with nuclear receptors providing well-studied examples. RARs and thyroid hormone receptors (T_3 Rs) are representative of a subset of nuclear receptors that bind to response elements in target genes as heterodimers with RXRs in the presence or absence of ligands. In the absence of ligand, retinoic acid and thyroid hormone receptors recruit NCoR/SMRT corepressor complexes through Cornr-box interactions and actively repress transcription. Ligand binding leads to an exchange of NCoR/SMRT complexes for coactivator complexes and transcriptional activation (Chen and Evans 1995; Horlein et al. 1995; Heinzl et al. 1997; Alarid et al. 1999; Privalsky 2004). Although the ligand-induced allosteric change in the AF2 helix of nuclear receptors is sufficient to inhibit corepressor binding and enhance coactivator interactions *in vitro*, the ligand-dependent switch of NCoR/SMRT corepressor complexes for coactivator complexes in cells has been suggested to require an active exchange mechanism (Perissi et al. 2004). Biochemical purification of HDAC3 or NCoR complexes has defined HDAC3, GPS2, and the transducin β -like factors TBL1 and TBLR1 as core components of larger NCoR/SMRT holocomplexes (Figs. 2, 5; for review, see Perissi et al. 1999; Li et al. 2000; Underhill et al. 2000; Guenther et al. 2001; Zhang et al. 2002; Yoon et al. 2003a; Perissi et al. 2004), and these

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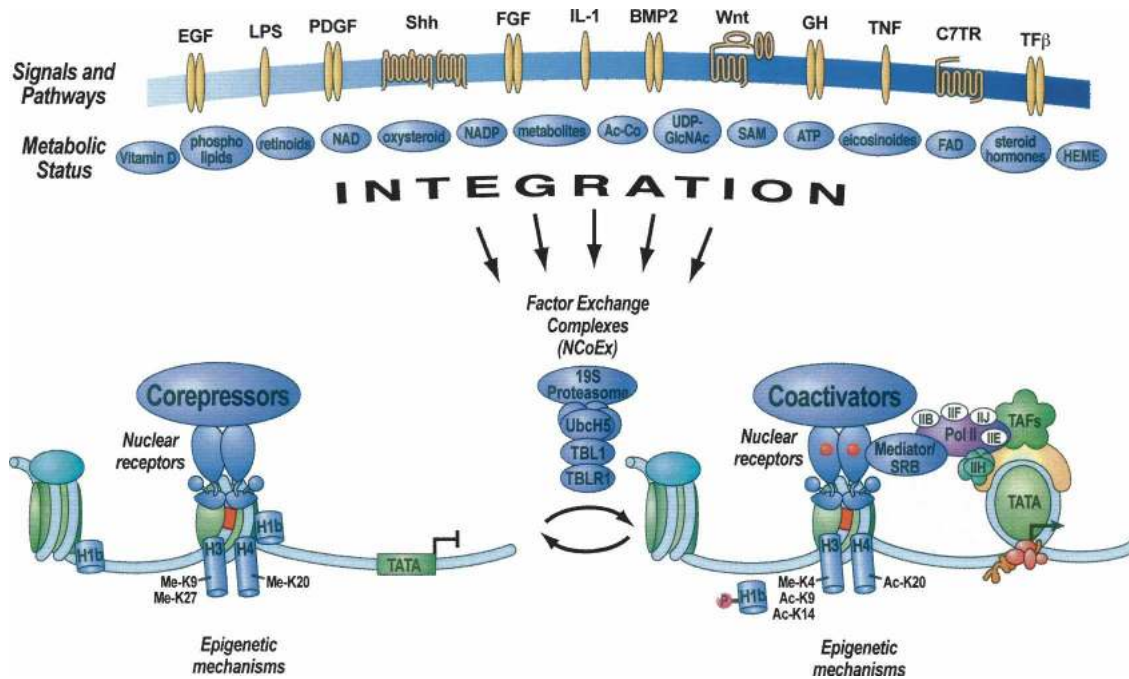


Figure 5. Corepressor/coactivator exchange complexes are targets of multiple extracellular and intracellular signaling pathways. For many signal-dependent transcription units, transcriptional activation requires active removal of corepressors in addition to recruitment of coactivators. In the case of nuclear receptors, TblR1 is used as a sensor of ligand binding, which activates its E3 ubiquitin ligase activity and leads to the ubiquitylation, clearance, and most likely proteasome-dependent degradation of corepressor complexes. Corepressor clearance results in gene derepression and is a prerequisite to the subsequent recruitment of coactivator complexes. This corepressor/coactivator exchange is mechanistically linked to changes in histone marks; for example, loss of histone H3-K9 and K27 methylation and gain of H3K9 and K14 acetylation. The factor exchange complexes themselves are proposed to represent targets of regulation, enabling an additional level of integration of multiple signaling inputs.

factors can all be identified on promoters subject to repression by unliganded retinoic acid or thyroid hormone receptors. The histone deacetylase activity of HDAC3 is essential for repression, and its activity is dependent on the allosteric properties of NCoR/SMRT. Additional low-affinity components, including Sin3A, HDAC1,2, and the Brg1 complex (Ayer et al. 1995), also contribute to NCoR/SMRT-dependent repression (Heinz et al. 1997; Zhu et al. 2006). Biochemical association of mSin3A/HDAC with Brg1 and hBrm-based SWI/SNF complexes suggests that these histone-modifying and chromatin remodeling activities are functionally required for transcriptional regulation (Sif et al. 2001). This finding indicates that corepressors can inhibit transcription by targeting complexes with dual functions, which can both alter nucleosome structure and deacetylate histones. It is reasonable to speculate that the Sin3A/B and BRG1 complexes can probably contribute to the repression mediated by the NCoR/SMRT/TBL1/TBLR1 holo-complex in part by stabilizing corepressor interactions with chromatin (Torchia et al. 1997; Li et al. 2000; Underhill et al. 2000; Humphrey et al. 2001; Yoon et al. 2003a; Nettles et al. 2004; Tomita et al. 2004). Intriguingly, TBL1 and TBLR1 components of the holo-complex have proven to be functionally required for the ligand-dependent dismissal of NCoR/SMRT from T_3R - and RAR-regulated transcription units based on their ability

to serve as E3 ubiquitin ligase adaptors for the recruitment of specific ubiquitylation machinery (Figs. 5, 6), and probably also for the proteasome-dependent degradation of the corepressors (Perissi et al. 2004). While TBLR1 (Dong et al. 1999; Boulton et al. 2000; Matsuzawa and Reed 2001; Perissi et al. 2004) selectively mediates the mandatory exchange of the key NCoR complex for coactivators on ligand binding, the critical target of TBL1 in the holo corepressor complex is still unknown.

Interestingly, other factors that function as specific regulated E3 ligases for the recruitment of dedicated ubiquitin conjugating/19S proteasome machinery could also be involved in clearing corepressor complexes and allowing for the subsequent engagement of coactivator complexes (Yoon et al. 2003a). The yeast ortholog of RPF1/NEDD E3 ligase RSP5 can potentiate progesterone and glucocorticoid receptor activation (Li and Rechsteiner 2001). The homologous E3 ligase E6 AP (Nawaz et al. 1999) similarly plays a role in activation by several nuclear receptors, although it is not clear whether its enzymatic function is required. In addition to UBCH5, UBCH7 is also required for ER α -, RAR-, and T_3R -dependent transcription events (Perissi et al. 2004; Dennis and O'Malley 2005).

A similar requirement for signal-dependent release of NCoR/SMRT corepressor complexes has been noted for genes regulated by activator protein 1 (AP1) and NF- κ B

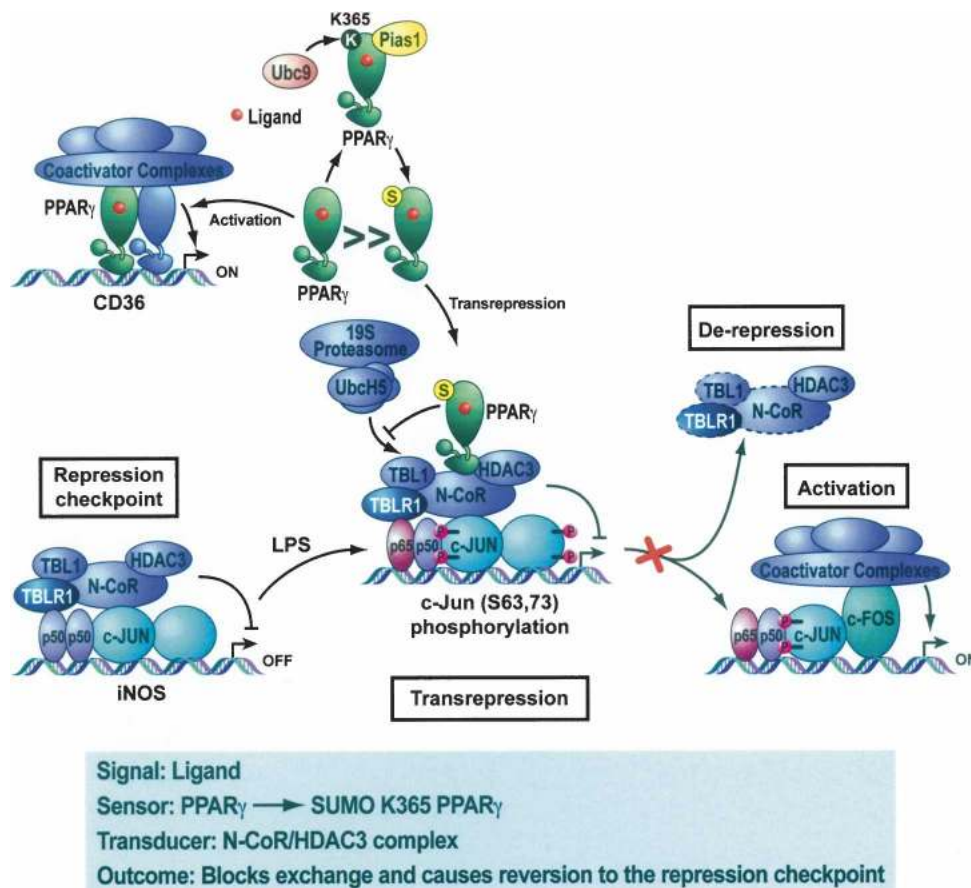


Figure 6. Corepressor/coactivator exchange as a target for integration of multiple signaling inputs. Under basal conditions, NCoR/HDAC3/TBL1/TBLR1 complexes are associated with a subset of promoters of inflammatory response genes through interactions with c-Jun homodimers, NF- κ B p50 homodimers and perhaps other sequence-specific DNA-binding factors. Proinflammatory signals, such as LPS, lead to activation of TBL1/TBLR1 E3 ligase activities and recruitment of the UbcH5 ubiquitylation machinery that mediates clearance of the NCoR complex. This, in turn, allows recruitment of c-Jun/c-Fos and/or p50/p65 heterodimers, coactivator recruitment, and transcriptional activation. In the presence of concurrent activation of PPAR γ , a subfraction of PPAR γ interacts with the SUMO E3 ligase PIAS1 and is sumoylated on K365 of the LBD. This, in turn, targets PPAR γ to NCoR/HDAC3/TBL1/TBLR1 corepressor complexes, where it prevents UbcH5-dependent ubiquitylation. As a consequence, NCoR corepressor complexes remain bound and continue to actively repress transcription. The fraction of PPAR γ that is not sumoylated can heterodimerize with retinoid X receptors and activate genes, such as CD36, that contain PPAR γ response elements. In this example, the second signal (ligand) is sensed by PPAR γ , leading to its SUMOylation. The transducer of this modification is the NCoR complex, which is now resistant to ubiquitylation-dependent turnover. The functional outcome is blockade of corepressor exchange and transrepression of the transcriptional response to LPS.

(Fig. 6; Hoberg et al. 2004; Ogawa et al. 2004; Perissi et al. 2004). In macrophages, several AP-1 and NF- κ B target genes proved to be occupied by NCoR/HDAC3/TBL1/TBLR1 corepressor complexes under basal conditions. These complexes were required to mediate basal repression because deletion of the NCoR gene resulted in de-repression of broad sets of AP-1 and NF- κ B target genes and the acquisition of a partially activated phenotype in the absence of an inflammatory stimulus (Ogawa et al. 2004). NCoR complexes were recruited to several AP-1 target genes through interactions with the c-Jun dimer. Signal-dependent activation of JNK and phosphorylation of c-Jun resulted in recruitment of the ubiquitin Ubc5/19S proteasome complex, followed by exchange of the NCoR corepressor for c-Jun/c-Fos heterodimers and as-

sociated coactivators (Fig. 5). Mutation of the JNK phosphorylation sites in the N terminus of c-Jun prevented corepressor exchange, thus suggesting a model in which c-Jun phosphorylation results in a conformational change in TBL1 or TBLR1 required for the recruitment of the ubiquitin-conjugating machinery (Ogawa et al. 2004).

NF- κ B-activated genes that are targets of NCoR/SMRT/HDAC3/TBL1/TBLR1 complexes under basal conditions include inducible nitric oxide synthase (iNOS). Activation of iNOS by the Toll-like receptor 4 (TLR4) agonist LPS resulted in clearance of the NCoR complex, dependent on the actions of TBL1, TBLR1, and Ubc5. NF- κ B target genes are also activated in response to cellular attachment to extracellular matrix as a criti-

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cal antiapoptotic signaling pathway. In this case, cell attachment was shown to stimulate IKK α -dependent phosphorylation of SMRT. This, in turn, led to ubiquitylation of SMRT, its dismissal from NF- κ B-regulated promoters, and nuclear export (Ting et al. 2002) as a prerequisite to NF- κ B-dependent gene activation. These findings are consistent with the observation that the ubiquitin-dependent dismissal and degradation of corepressors is required for the switch from gene repression to gene activation (Yoon et al. 2003b), and supports the previous observations that protein phosphorylation is commonly used to mark proteins for ubiquitylation by SCF E3 ligase complexes (Hermanson et al. 2002).

The possibility of regulating the localization of corepressors in the cell by nuclear export in response to specific signals raises the interesting question of whether NCoR/SMRT degradation occurs in nuclei in the vicinity of the target promoter, or whether its dismissal is coupled with a relocalization event (possibly associated with chaperones such as 14-3-3 proteins) that confines NCoR/SMRT degradation either to the cytoplasm or to distal nuclear location "nuclear storage" compartments. As NCoR/SMRT corepressor complexes are found on only a subset of NF- κ B- and AP-1-responsive genes, it remains possible that other corepressor complexes will prove to mediate basal repression of other subsets of genes activated by these factors. In concert, studies of nuclear receptor-, NF- κ B-, and AP-1-dependent transcription units indicate that for many genes, signal-dependent transcriptional activation involves corepressor clearance and promoter derepression as a prerequisite to activator/coactivator binding and full transcriptional activation.

Molecular sensors for interpretation of transcriptional regulatory signals

Based on the evidence reviewed above, it is now clear that coregulatory complexes and the mechanisms that mediate their exchange are targets of regulation. Furthermore, the ability of these complexes to serve as molecular sensors of multiple signaling inputs enables them to play essential roles in integration of transcriptional responses. Here we describe several examples of these molecular sensing strategies.

Calcium sensor

A covalent modification recently linked to transcription is poly(ADP-ribosyl)ation of proteins mediated by the poly(ADP-ribose) polymerase 1 (PARP1) enzyme. PARP1 catalyzes the transfer of ADP-ribose chains onto glutamic acid residues of acceptor proteins, including itself (automodification), histones, transcription factors, and DNA repair proteins using NAD⁺ as a substrate involved in chromatin decondensation, DNA replication, and DNA repair. Therefore, poly(ADP-ribosyl)ation by PARP1 affects cellular processes such as apoptosis, necrosis, cellular differentiation, malignant transformation (for review, see D'Amours et al. 1999), and modulation of

transcription factors (Plaza et al. 1999; Akiyama et al. 2001; Hassa and Hottiger 2002). PARP influences both the expression and silencing of genes at diverse times during *Drosophila* development (Tulin et al. 2002); it has been demonstrated that high PARP enzymatic activity is observed in areas of high transcriptional activity and chromatin decondensation on the polytene chromatin (Taniguchi et al. 1982; Tulin et al. 2002). Recent studies have also suggested a role for PARP1 as a coregulator for activation of estrogen, thyroid, and retinoic acid receptor-dependent transcription (Kim et al. 2004; Pavri et al. 2005). PARP1 can be viewed as a platform protein, based on its ability to physically interact with the mediator complex (Pavri et al. 2005) and as a "molecular sensor" based on activation of its enzymatic function in the context of Groucho/TLE-corepressor complex by calcium-dependent protein kinase, CaMKII δ (Ju et al. 2004). Recently published data indicate that it is likely that PARP1 interaction is critical for conversion of Mediator to its active conformation in the case of RAR-mediated transcription (Pavri et al. 2005), and for the switch in the function of HES1 bHLH transcription factor from a Groucho/TLE-dependent repressor to an activator, required for neuronal differentiation of PDGF-stimulated neural stem cells (Ju et al. 2004). PARP1-dependent dismissal of components of the Groucho/TLE-corepressor complex from target genes, such as HES1-regulated promoters (Fig. 7), strongly depends on triggering the poly(ADP-ribosyl)ation activity of PARP by a specific signaling pathway. However, its action in the Mediator complex has been suggested to be independent of PARP enzymatic function (Pavri et al. 2005), despite the fact that transcription activated by the estrogen receptor has been reported to require PARP1 enzymatic activity (Kim et al. 2004, 2005b). In the case of retinoid acid-regulated gene transcription, it has been shown that PARP1 functions at a step prior to association of TFIID and Mediator with promoter sequences in the *in vitro* transcription reconstitution assay (Pavri et al. 2005); therefore, it is highly possible that the mode of PARP1 action could be dependent on the actions of different temporal components order of the events serially required for transcriptional initiation, elongation, and termination.

Sensor strategies in transrepression

Signal-dependent repression of gene transcription is an essential characteristic of gene networks that control complex developmental, homeostatic, reproductive, and immunological programs of gene expression. Negative regulation of inflammatory responses by nuclear receptors has been intensively studied because of the key role of inflammation in both immunity and the pathogenesis of chronic disease that include atherosclerosis (Libby and Theroux 2005), diabetes (Wellen and Hotamisligil 2003), and neurodegenerative diseases (Carson 2002). Many nuclear receptors are capable of negatively modulating the magnitude of transcriptional responses to activating signals, including the glucocorticoid receptor (Jonat et al. 1990; Schule et al. 1990; Ray and Prefontaine 1994), es-

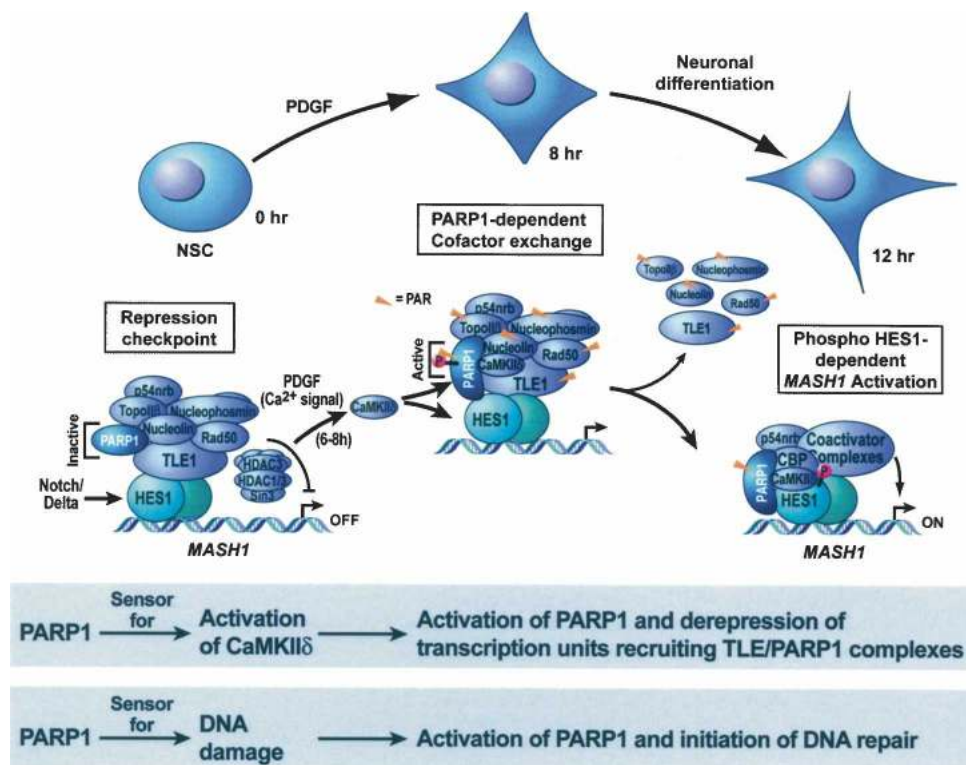


Figure 7. PARP-1 as a cofactor for calcium-dependent signaling pathway during neurogenesis. The HES1 repressor recruits a Groucho/TLE/PARP-1 complex to the MASH-1 promoter. Induction by a neurogenic signal up-regulates expression of CAMKII- δ , which induces PARP-1 enzymatic activity, required for removal of corepressor complex from the MASH-1 promoter. Both PARP-1 and CAMKII- δ remain bound to the promoter, and CAMKII- δ -dependent phosphorylation of HES1 results in coactivator complex recruitment and transcriptional induction.

trogen receptor, PPARs (Jiang et al. 1998; Ricote et al. 1998; Staels et al. 1998; McKay and Cidlowski 1999; Lee et al. 2003), and LXRs (Joseph et al. 2003). This activity does not generally require sequence-specific DNA binding, and is referred to as transrepression. Recent studies indicate that different nuclear receptors are capable of repressing overlapping but distinct sets of inflammatory response genes, and that the sensitivity of a particular gene to repression is influenced by the activating signal (Ogawa et al. 2005). Furthermore, transrepression mediated by several different nuclear receptors has been demonstrated to be selective for specific subsets of genes that are activated by a particular activating signal, implying a requirement for context/promoter-specific mechanisms (De Bosscher et al. 2003; Luecke and Yamamoto 2005; Ogawa et al. 2005). Here we focus on reviewing recent studies that connect nuclear receptor transrepression mechanisms to coactivator/corepressor exchange/recruitment and provide potential insights into how periodic sensing mechanisms might be used in a combinatorial manner.

Signal-dependent activation of inflammatory programs of gene expression by pathogens or endogenous mediators is highly dependent on NF- κ B and AP-1 family members (Karin and Greten 2005). In contrast to nuclear receptors, in which the precise, ligand-dependent, temporal associations of large numbers of functionally dis-

tinct and required coactivator complexes have been extensively documented, the range of coregulator requirements and the temporal nature of their associations with specific NF- κ B and AP-1 target genes remain less well established (Hassa et al. 2005). Many AP-1 and NF- κ B target genes are occupied in the basal state by NCoR/SMRT corepressor complexes, and perhaps other corepressors, that must be cleared in a signal-dependent manner as a prerequisite for transcriptional activation. Similarly, many factors initially described as nuclear receptor coactivators have been demonstrated to function as coactivators of NF- κ B and AP-1 (Janknecht and Nordheim 1996b; Gerritsen et al. 1997; Baumeister et al. 1998; Lee et al. 1998; Na et al. 1998; Zhong et al. 1998; Baek et al. 2002; Covic et al. 2005). Furthermore, recent studies of NF- κ B-dependent activation of the *cIAP2* gene revealed a periodic cycle of SMRT/HDAC3 binding and dismissal followed by p53/p300 recruitment and dismissal with a periodicity of \sim 40 min (Hoberg et al. 2006). While the generality of this phenomenology remains to be established, the observation that a significant number of inflammatory response genes are occupied in the basal state by NCoR/SMRT complexes is consistent with the possibility that signal-dependent activation of these genes will require a highly choreographed sequence of events beginning with corepressor clearance followed by sequential recruitment of coactivators that act combina-

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torially to stimulate gene transcription. Consistent with this, recent studies suggest that PARP1 can act as a promoter-specific coactivator of NF- κ B in vivo by interacting with p300 and the p65 and p50 subunits of NF- κ B (Covic et al. 2005). PARP1 is acetylated by p300/CBP in response to inflammatory stimuli, which is required for it to interact with NF- κ B subunits and function in a synergistic manner with p300 and the Mediator complex. Interestingly, PARP1 also interacts with HDACs1-3, suggesting a model in which PARP1 functions as a coactivator/corepressor exchange complex on inflammatory response genes, depending on its acetylation status.

Given this scenario, it is reasonable to speculate that any essential step in the corepressor/coactivator cycle required for gene activation is also a potential target for physiological counter-regulation. For example, blockade of specific coactivator interactions or inhibition of corepressor clearance is predicted to result in antagonism of signal-dependent activation. In this context, promoter- or signal-specific utilization of particular coactivators or corepressors would provide the basis for specific patterns of repression. The ability of a nuclear receptor to inhibit inflammatory responses by preventing signal-dependent corepressor dismissal has recently been reported in the case of PPAR γ (Ogawa et al. 2005). Treatment of macrophages with a PPAR γ agonist prevented the clearance of NCoR corepressor complexes from several NF- κ B target genes in response to an inflammatory stimulus. In this case, ligand binding promoted sumoylation of a specific residue in the LBD of PPAR γ that enabled it to bind to NCoR corepressor complexes on the promoters of these genes. This, in turn, prevented the signal-dependent recruitment of ubiquitylation machinery that is normally required for corepressor clearance. As a result, NCoR complexes remained bound to their target promoters and maintained these genes in a repressed state. The presence of NCoR complexes on some, but not all, inflammatory promoters provides at least a partial explanation for the promoter specificity of PPAR γ -dependent transrepression.

Transrepression pathways

Selective targeting of specific coactivators can also provide the basis for nuclear receptor-mediated transrepression. Promoter- and signal-specific utilization of coactivators has recently been established for several NF- κ B target genes. Specific sequences of κ B elements determine whether or not interferon regulatory factor 3 (IRF3) is used as a required coactivator for NF- κ B-dependent activation (Fig. 8; Leung et al. 2004). Conversely, the p65 component of NF- κ B has been demonstrated to be required as a coactivator of IRF3 target genes in response to TLR4 activation, but not TLR3 activation (Fig. 8; Wietek et al. 2003). IRF3 and p65 interact biochemically, and the binding of the glucocorticoid receptor to p65 blocks this interaction (Ogawa et al. 2005). Activation of the glucocorticoid receptor thus represses the subset of NF- κ B target genes that require IRF3 as a coactivator as well as IRF3 target genes that require p65 as a coactivator when

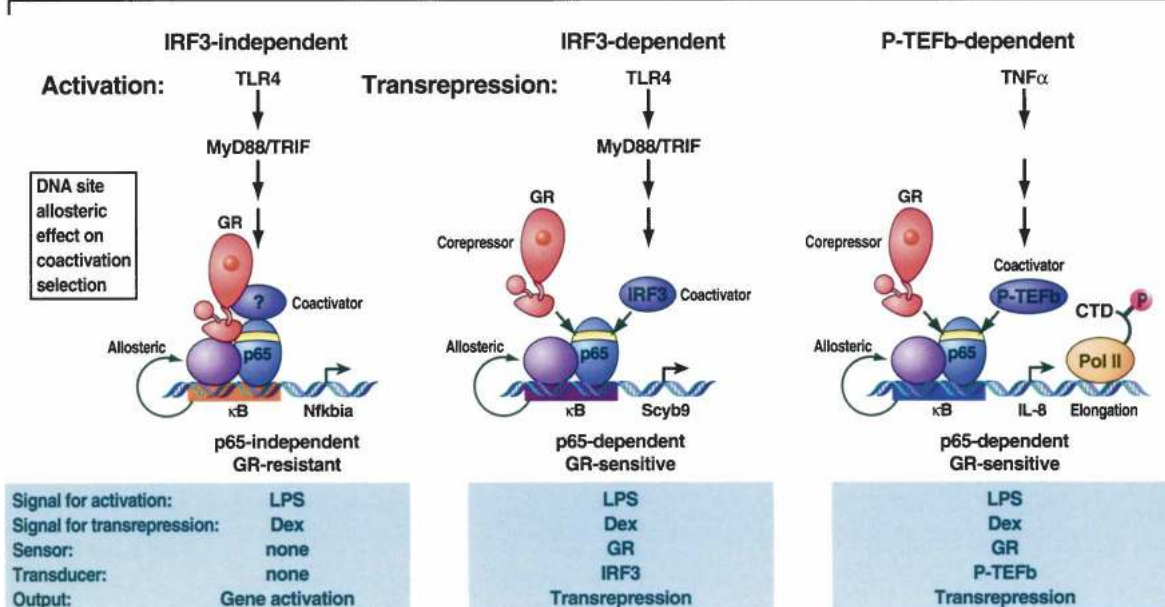
activated by TLR4. In contrast, IRF3 target genes become glucocorticoid resistant in response to TLR3 activation due to the lack of a requirement for p65 for IRF3 function (Fig. 8; Ogawa et al. 2005).

An analogous mechanism accounts for promoter-specific repression of TNF α -inducible genes. TNF α induces *Nfkbai* and *IL8* transcription in A543 cells, but only *IL8* is sensitive to GR-mediated repression. This has been related to a requirement of NF- κ B for P-TEF β as a required coactivator for *IL8* induction, but not for *Nfkbai* induction (Luecke and Yamamoto 2005). GR is tethered to both the *IL8* and *Nfkbai* promoters in a ligand-dependent manner, but by disrupting P-TEF β /NF- κ B interactions on the *IL8* promoter, blocks TNF α -induced activation (Fig. 8). Intriguingly, P-TEF β functions at a post-transcriptional step by phosphorylating the CTD of Pol II.

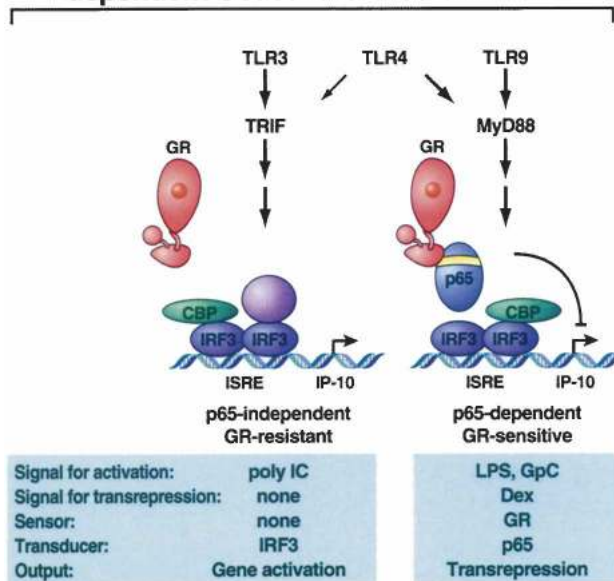
A mechanistically distinct example of GR/coactivator interactions that result in transrepression has been reported involving the p160/SRC family member, GRIP-1 (Fig. 8; Rogatsky et al. 2001). In U2OS osteosarcoma cells, the *collagenase 3* gene is activated by phorbol esters through an AP-1 element, and glucocorticoid receptor agonists repress this response. Activation of GR causes it to be tethered to the AP-1 element and to recruit GRIP1, which in this context functions as a corepressor. The corepressor function of GRIP1 is dependent on an intrinsic repression domain that is not shared by the other p160/SRC family members. This domain enabled GRIP1 to potentiate GR-mediated transrepression of NF- κ B-dependent gene expression. In contrast, repression by T $_3$ R was unaffected by GRIP1. These findings indicate that the composition of regulatory complexes, and the biological activities of the bound factors are dynamic and dependent on cell and response element contexts. Consistent with this, both GRIP1 and SRC-1 have recently been shown to promote GR-mediated repression of TGF β -induced *PAI-1* expression.

An additional example of the diverse molecular mechanisms of transrepression is provided by the *25(OH)D3 1 α -hydroxylase* gene [*1 α (OH)ase*], which encodes a key enzyme in the production of vitamin D, and is subject to transrepression by the vitamin D receptor (VDR) (Takeyama et al. 1997). Activation of the *1 α (OH)ase* promoter is dependent on promoter binding of a bHLH transcriptional activator, VDR (Murayama et al. 2004). PKA phosphorylation of VDR recruits p300 coactivator complexes that acetylate histone tails of surrounding nucleosomes, binding the WINAC chromatin remodeling complex through the bromodomain of its WSTF component, tethered to the *1 α (OH)ase* promoter by interaction with unliganded VDR. This establishes a transition state in which the promoter is active, but poised for repression. Binding of active vitamin D to the VDR results in the recruitment of NCoR/SMRT/HDAC complexes to the *1 α (OH)ase* promoter and deacetylation of surrounding nucleosomes. This results in activation of chromatin remodeling activity of the WSTF complex and active repression of the *1 α (OH)ase* promoter (Fujiki et al. 2005). These findings suggest that the interaction

Transrepression by Coactivator Competition Based on Allosteric Effect in the DNA Site



Transrepression by Blocking Signal-dependent Coactivator Recruitment



Transrepression by Protein-dependent Allosteric Control of Coregulator Conformation

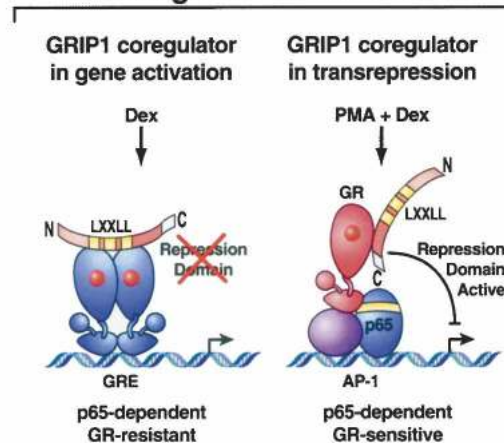


Figure 8. Gene-specific and signal-specific transrepression of inflammatory responses by the glucocorticoid receptor. (*Top panels*) The specific sequences of NF- κ B-binding sites dictate promoter-specific requirements for IRF3 or P-TEFb as coactivators of p65. By binding to p65, the GR blocks IRF3 interactions, resulting in transrepression of the subset of NF- κ B genes that require these factors, but not genes that are IRF3- or P-TEFb-independent. (*Bottom left panel*) Model for signal-specific glucocorticoid receptor-mediated transrepression of IRF3 target genes. IRF-mediated activation of direct target genes in response to TLR4 and TLR9 agonists uses MyD88 as a signaling adapter protein that imposes a requirement for p65 as a signal-specific coactivator. The p65/IRF interaction is disrupted by liganded glucocorticoid receptor, resulting in transrepression. TLR3-specific activation of IRF through the TRIF pathway does not require p65, and is therefore GR-resistant. (*Bottom right panel*) The p160 factor GRIP1 functions as a GR coactivator on genes containing positive GREs, but is converted to a corepressor when GR is tethered to AP-1 sites through the context-specific utilization of an intrinsic repressor domain that is specific for GRIP1.

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of VDR with the WINAC complex dictates the context-dependent recruitment of NCoR/SMRT complexes in response to an activating ligand and corepressor/coactivator exchange.

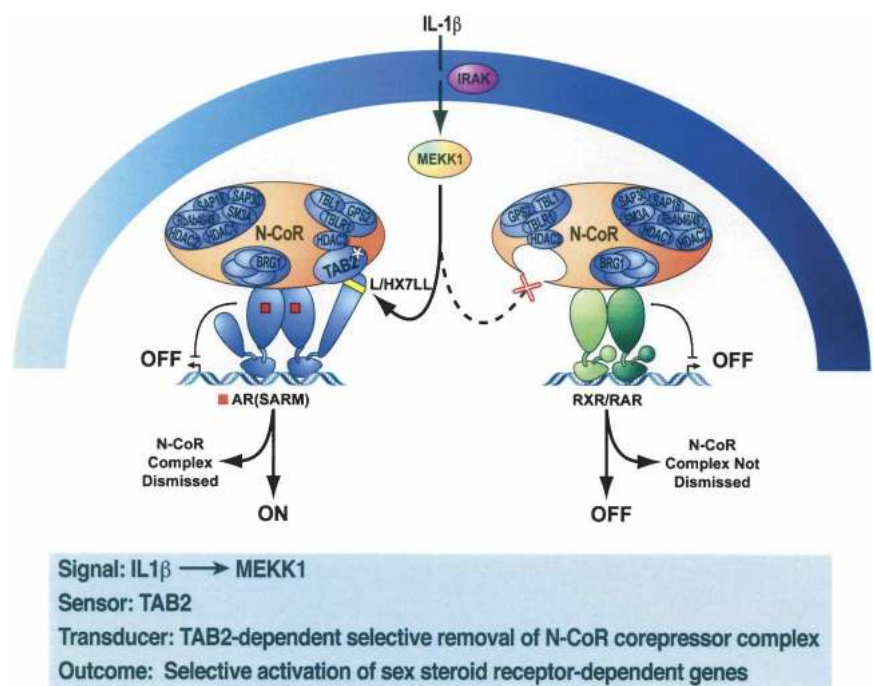
Components of cofactor complexes as sensors for inflammatory signals in cancer

A third example of the specificity of sensor systems has been provided by decoding the pathway linking inflammatory signals to a specific nuclear receptor derepression strategy. This, for example, operates for clinically used selective androgen/estrogen receptor antagonist/modulators (SARMs/SERMs). While SARMs are initially effective in treatment of prostate cancer, there is a rapid invariant resistance with progression from androgen-dependent to androgen-independent growth. While many specific models have been proposed (Feldman and Feldman 2001; Chen et al. 2004; Debes and Tindall 2004), one component may be related to inflammatory signals from macrophages based on direct cell–cell adhesion between macrophages and prostate cancer cell lines. For a subset of NF- κ B/p50 regulated genes, including a key metastasis suppressor gene in prostate cancer, *KAI1* (Baek et al. 2002), IL1-dependent dismissal of the NCoR complex interaction with p50 dimers proved to be dependent on activation of MEKK1 and on the presence of a component of the NF- κ B activation machinery, TAB2 (Baek et al. 2002). Activation of *KAI1* is dependent on recruitment of the Tip60 coactivator complex (Baek et al. 2002), and an alteration in the ratio of Tip60: β -catenin that can reverse *KAI1* expression, occurring in more aggressive prostatic tumors (Kim et al. 2005a; Ogawa et al. 2005), which is based on selective recruit-

ment of a reptin chromatin remodeling complex with β -catenin, that functions to cause β -catenin-dependent repression in both prostate cancer and in orchestration of mammalian organogenesis (Olson et al. 2006). Thus, a component of the NF- κ B pathway, TAB2 (Zhu et al. 2006), has proven to be a molecular beacon for actions of MEKK1 in response to cytokines (Fig. 9).

Macrophage/cancer cell interactions cause a switch in the function of SARMs from repression to activation due to the selective presence of an evolutionarily conserved receptor N-terminal helical motif (L/HX₇LL) in sex steroid receptors, as well as in Bcl3 (Zhu et al. 2006), but not in other nuclear receptors. This helix has proved to be required for recruitment of a factor related to the NF- κ B pathway, TAB2, as a component of the NCoR corepressor complex, based on a ternary L/HX₇LL TAB2 NCoR complex (Baek et al. 2002). TAB2 acts as a sensor for inflammatory signals serving as a molecular beacon for recruitment of a protein kinase, MEKK1 activated by the inflammatory cytokine, which, in turn, mediates dismissal of the NCoR complex, permitting a clinically undesirable derepression of androgen and estrogen receptor target genes. Comparison of targets by genome-wide analyses of ER α and AR promoter occupancy “negatively” regulated gene targets, provided initial evidence that this strategy appears to have been evolutionarily selected to mediate reversal of “negative” gene regulation by sex steroid receptor agonists, particularly those that may be associated with reproductive biology, including BMP7, the ABCG2 transporter, and Bcl3, as well as several cofactor-encoding genes (Glass and Rosenfeld 2000; Zhu et al. 2006). This conserved sensor strategy may function to mediate reversal of sex steroid-dependent repression of a limited cohort of target genes in

Figure 9. Use of components of the NF- κ B pathway as a molecular sensor of the IL-1 β -sensitive derepression. In the presence of SARM, AR recruits NCoR holorepressor complex. The evolutionarily conserved N-terminal sequence “L/HX₇LL” permits recruitment of TAB2 to the receptor/TAB2/NCoR ternary complex. TAB2 functions as a molecular sensor, which permits IL-1 β -dependent corepressor dissociation based on the phosphorylation of TAB2 by MEKK1. Other nuclear receptors are resistant to this derepression because TAB2 is not corecruited to the NCoR holocomplex.



response to inflammatory signals. Interestingly, even when SERMs/SARMs cause gene activation, there is a limited, but distinct cohort of activated targets, and a distinct set of coactivators is no longer required, such as for inflammatory cytokine-mediated activation (Chen et al. 2004).

Conclusions

The rapid acceleration in the scope of knowledge of the coactivator/corepressor network of regulatory complexes, the discovery of a temporal/spatial pattern of their exchange, and development of the histone code as a three-dimensional matrix for factor recruitment have together provided insights into the coordinated fashion in which DNA-binding transcription factors and coregulatory mechanisms are biochemically linked to orchestrate programs of regulated gene expression. Covalent modifications resulting from specific signaling cascades can provide a switch in activity of each coregulatory complex, permitting adjustment (integration) of transcriptional output to the diverse, ever-changing cellular signaling environment. In concert with the many protein-protein interaction motifs in various coactivators/corepressors, many of which recognize specific histone/factor modifications, we can begin to reconstruct the "code" for each cofactor and histone modification that constitutes the cycle for regulated gene activation.

We believe that future years of molecular and structural studies in this direction will propel discovery of many unexpected aspects of the diverse roles for nuclear coregulators in sensing, interpreting, and transmitting the complex regulatory signals designed by nature in order to provide the multitude of required cell-specific transcriptional programs.

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