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Nuclear Receptor Coregulators and Human Disease

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Nuclear receptor (NR) coregulators (coactivators and corepressors) are essential elements in regulating nuclear receptor-mediated transcription. In a little more than a decade since their discovery, these proteins have been studied mechanistically and reveal that the regulation of transcription is a highly controlled and complex process. Because of their central role in regulating NR-mediated transcription and in coordinating intercompartmental metabolic processes, disruptions in coregulator biology can lead to pathological states. To date, the extent to which they are involved in human disease has not been widely appreciated. In a complete literature survey, we have identified nearly 300 distinct coregulators, revealing that a great variety of enzymatic and regulatory capabilities exist for NRs to regulate transcription and other cellular events. Here, we substantiate that coregulators are broadly implicated in human pathological states and will be of growing future interest in clinical medicine. (*Endocrine Reviews* 28: 575–587, 2007)

I. Introduction

COREGULATOR BIOLOGY RESTS upon the shoulders of a long history of research on nuclear receptors (NRs) and their ligands. NRs are members of a large superfamily of ligand-regulated (and orphan) transcription factors that play a central role in the body's ability to transduce steroid, retinoid, thyroid, and lipophilic endocrine hormones. Seminal work in the 1960s and 1970s dealt with determining how these hormones, characterized decades before, elicited their physiological actions. This led to the identification of NRs as their cognate ligand-activated DNA-binding transcription factors (1, 2). A broad range of physiological processes are regulated through these endocrine signals in conjunction with their 48 receptors in humans. For example, the androgen receptor (AR), progesterone receptor (PR), and estrogen receptors (ERα and ERβ) play central roles in reproduction and target tissue growth; the glucocorticoid receptor (GR) in glucose metabolism, inflammation, and stress; thyroid hormone receptors (TRs) in oxidative metabolism; and peroxisome proliferator-activated receptors (PPARs) in lipid and energy metabolism. A large variety of synthetic ligands have been designed to pharmacologically target these NRs, finding widespread clinical use.

As transcription factors, NRs have a nearly direct role in regulating the expression of hormone-response genes. This regulatory capacity of NRs occurs through their ability to recognize specific sequences in the promoters of their target genes and their relationships with the RNA polymerase II (pol II) holocomplex and the chromatin environment that surrounds these genes (3). Central to our discussion here, coregulators (coactivators and corepressors) more directly influence these critical regulatory aspects of global gene expression. We define coactivators as molecules that are directly recruited by NRs to enhance NR-mediated gene expression (4). Recruitment is usually, but not always, ligand dependent. Coactivators can be subdivided into two groups: primary coactivators and secondary coactivators. Secondary co-coactivators represent a subgroup of molecules that are constituents of multisubunit coactivator complexes (see *Section III*) and that also contribute to the enhancement of NR-mediated transcription, but do not directly contact the NRs. Corepressors act in an opposite manner to repress gene expression, primarily through their interaction with unliganded NRs (5). Depending upon cell and signaling context, coactivators and corepressors sometimes can switch roles. Presently, approximately 285 coregulators are reported in the literature, frequently in connection with numerous physiological functions and pathological states. Here, we will emphasize that coregulators are broadly implicated in an unexpectedly wide variety of human disease states and are becoming of increasing interest in clinical medicine.

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Abbreviations: AIS, Androgen insensitivity syndrome; AR, androgen receptor; CBP, cAMP response element-binding protein binding protein; C/EBPβ, CAAT enhancer binding protein-β; ER, estrogen receptor; GR, glucocorticoid receptor; GTF, general transcription factor; HDAC, histone deacetylase; N-CoR, nuclear receptor corepressor; NR, nuclear receptor; PGC-1α, PPARγ coactivator-1α; pol II, polymerase II; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; RIP140, receptor-interacting protein 140; SNP, single nucleotide polymorphism; SRC, steroid receptor coactivator; TR, thyroid hormone receptor.

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II. History of Coregulators

The regulation of mRNA transcript production by RNA pol II is a central biological theme that remains the subject of strong ongoing interest because the expression of all mammalian proteins depends upon the interaction of pol II with the genome. Pol II is a large multisubunit protein complex, consisting of a constitutive set of approximately 30 general transcription factors (GTFs) that provide for a large degree of regulatory complexity (6–8). Experiments initially done in yeast brought us the realization that, in addition to these core GTFs, an additional set of helper proteins assist in communication between transcription factors and the pol II complex. They were originally envisioned to function primarily as "transcriptional adaptors," bridging DNA binding transcription factors to the general transcription machinery (9, 10). Unlike GTFs, coactivators interact directly or in close association with the DNA-binding transcription factors and are not constitutive members of the pol II holocomplex. Corepressors, on the other hand, were predicted to exist based upon the ability of the unliganded TR to function as a transcriptional repressor (10). Corepressors thus function as counterparts to coactivators, revealing that NR-mediated transcription is subject to both positive and negative regulation. As we shall discuss below, our appreciation of the wide array of mechanisms involved in regulating pol II-mediated transcription has come mainly from the characterization of these coregulators.

One of the first fruits that emanated from the identification of coregulators was that their primary amino acid sequence revealed a diverse array of enzymatic and functional events that control transcription, emphasizing that transcription is subject to a very complex sequence of events (11). Beyond being just "bridging" agents, coregulators possess numerous enzymatic capabilities and can act in many substeps of transcription, including transcriptional elongation, RNA splicing, and mRNA transport (12). Initially, after the identification of ERAP160, a protein that specifically interacts with agonist-bound receptor (13), the cloning of the first NR coactivator steroid receptor coactivator (SRC-1) (14), and the corepressors nuclear receptor corepressor (N-CoR) and silencing mediator of retinoid and TR (SMRT) (15, 16), we predicted that there would be perhaps 10 coactivators and a few corepressors in the cell. In contrast, nearly 300 coregulators have now been reported in the literature. Understanding the biological and clinical "footprint" of this ever-growing group of proteins represents a considerable challenge. In this review, we shall see that when taken as a whole, coregulators can be recognized as important and pervasive contributors to a wide array of human diseases.

The involvement of NRs in pathologies has long been known (17). In large part, this is more straightforward because NRs are classified upon the biological activities of their cognate ligands. For instance, the mineralocorticoid and glucocorticoid receptors have roles in mineral balance and glucose metabolism. In contrast, it is harder to understand how any given coregulator might contribute to pathology. In most cases, this is because coregulators do not possess strict specificity for a particular NR; instead their actions are pleiotropic, influencing the transcriptional output of a large number of transcription factors. Nevertheless, as we shall discuss in *Section IV*, rapid progress has been made in identifying coregulator-related diseases.

III. Emerging Aspects of Coregulator Biology

Core coregulators, those that interact directly with NRs, exist in large steady-state complexes with multiple secondary co-coregulator partners. Each component may possess multiple enzymatic capabilities such as acetyltransferase, methyltransferase, phosphokinase, ubiquitin ligase, and ATPase activities, ultimately making these complexes versatile enzymatic machines for regulating gene expression (12). Coregulator activity is directly affected by its phosphorylation, methylation, acetylation, or other modification status, forming a posttranslational modification code. This code then controls the coregulator's transcriptional activity and transcription factor preferences (18). As such, coregulators are "master genes" that become regulatory hubs for the coordinated control of broad transcriptional programs such as for cell growth, differentiation, and metabolic functions (19). For instance, SRC-3 is phosphorylated at distinct serine/threonine residues by a number of different kinases, generating a distinct phosphorylation code on the coactivator. This code is able to control the ability of SRC-3 to coactivate selectively NRs and non-NR transcription factors (20). Clinically, this phenomenon is likely to be important because overexpression of both SRC-3 and the human epidermal growth factor receptor (her-2/neu) kinase in human breast cancers correlates with decreased breast cancer survival, early tamoxifen resistance, and possible alterations in SRC-3 phosphorylation status (21, 22). The coregulators SMRT and N-CoR also are regulated by phosphorylation, controlling their intracellular localization (23, 24). Phosphorylation of either results in its redistribution to the cytoplasm, neutralizing their ability to corepress mRNA production in the nucleus (23). Kinase signaling systems and coregulators thus work hand-in-hand to regulate broad transcriptional programs in a concerted fashion.

High throughput genomic technologies such as mRNA gene expression profiling have been of great use in understanding how coregulator expression relates to human pathologies such as cancer (25–27). However, because most coregulators function as proteins, emerging proteomic technologies that can efficiently assess cellular coregulator protein levels will likely be more informative. It is well known through work in our laboratory and other groups that coregulators are subject to degradation by ubiquitin-dependent and -independent proteasome systems (4, 28). In normal tissues, most coactivators appear to be expressed in a constitutive manner at the mRNA level, and their mRNAs are not subject to dynamic regulation in response to acute external stimuli [PPARγ coactivator-1α (PGC-1) is a notable exception] (29); the pathological cell does not hold to this general role. Cellular coregulator content can be regulated at the protein level by posttranslational modifications, NR ligands, and other stimuli that influence their protein stability (30–32). Directly related to this, proteomic approaches to address coregulator posttranslational modifications also will

be crucial in accurately assessing the activity state of coregulators in the cell, something that cannot be accounted for in mRNA-based gene expression profiling studies.

Bioinformatics approaches promise to reveal a more complete picture of the role of coregulators in human disease. Because of their overarching and pleiotropic functions, recognizing coregulator involvement in pathological conditions will be challenging, something that broad inspection of cell- and genome-wide information may reveal more clearly. Other high throughput technologies include chromatin immunoprecipitation "ChIP on CHIP" assays, protein-interaction network maps, and gene polymorphism disease relationship studies (33). Although these types of approaches are applicable to the study of other proteins as well as coregulators, they should help us understand the role that coregulators play in human disease in much greater detail.

IV. Coregulator Involvement in Human Disease

Through a broad and extensive review of published literature on coregulators, we have identified nearly 300 coregulators. Many within the list are primarily recognized as coregulators, including SRC family proteins, PGC-1α, cAMP response element-binding protein binding protein (CBP), and others. On the other hand, a certain number of proteins in this list are not commonly thought of as such, like BRCA1 (34), p53 (35) and β-catenin (36) but are included if they have been reported to function as coregulators in addition to other biological roles. Overall, this constitutes a large number of coregulator proteins, enough to ask new questions about the overall scope of coregulators in human biology.

We have cited 102 unique coregulators that are involved in human diseases (Table 1). This includes all proteins reported to function as coregulators that are mutated, over- or underexpressed, or exist as pathological polymorphisms in actual human conditions. When tabulated into some common disease groupings, it can be seen that coregulators have primarily been reported in the literature as over- or underexpressed in cancers, which is to be expected because of clinical interest. Because coregulator levels in cells normally are tightly regulated and small changes can greatly influence function, we assume that over- or underexpression contributes to the associated pathology. For instance, one could anticipate that endocrine-related cancers (such as breast, uterine, and prostate cancers) might progress due to alterations in coregulator expression. It is only a matter of time until human investigations of coregulators are extended to all disease states.

Coactivator expression defects in immortalized human cell lines (such as MCF-7 or HeLa cells) are excluded here so as to stress the cases where coactivators have a more direct clinical relevance to human diseases. Due to the extent to which many of these proteins (p53 for instance) are involved in cancer and other factors regarding the nature of the coregulator disease studies, this list does not represent a complete account of all cases. However, it is patently clear that coregulators are involved in a broad range of pathologies as enumerated in *Section V* and in Table 1. From our survey, we are able to group coactivator-associated pathologies into a number of categories: *i.e.*, over- or underexpressed in cancer, metabolic syndromes, heritable syndromes, coactivator fusion proteins, and coactivator gene polymorphisms.

V. Coregulator Over- and Underexpressions in Cancer

Instances where coregulators are over- and underexpressed in human cancers make up the largest group of related diseases, where by our count, at least 102 different coregulators have been reported to be over-/underexpressed in the literature (Table 1). Coregulator overexpression may invoke carcinogenesis, enhance its progression, or in some cases, alter the biological activities of therapeutic NR ligands (37). Because coregulator misexpression is one obvious possible cause for endocrine-related cancers, numerous studies have sought and found such a relationship. In addition to this, many other cancers that do not immediately bring NRs or endocrine relationship to mind also are represented, indicating that coregulators are broadly involved in a much larger array of cancers than originally thought. This point is reinforced by an examination of coregulators in the cancer profiling Oncomine database (www.oncomine.org) (38). This database is a common repository for transcriptome meta-analysis of human cancers and tissues (see Ref. 39 for discussion on the limits and robustness of gene expression profiling). Overall, Oncomine data reveal that coregulators are broadly over- or underexpressed in human cancers (Table 2). For instance, in lung cancers, 60% of the coregulators we have identified in the literature are overexpressed, 38% in breast cancers, and 43% in prostate cancers. The Oncomine database also indicates that many coregulators are underexpressed in human cancers as well. Again, this is likely due to the pleiotropic capabilities of these proteins. For instance, by failing to stimulate the transcription of tumor-suppressing transcription factors such as p53 or the vitamin D and other repressive receptors, uncontrolled cell growth could ensue (40–42). Overall, given the bulk of cases in the literature and gene expression profile data meta-analysis, it is reasonable to think that coregulator misexpression is a pervasive agent in the progression (or etiology) of human cancers.

VI. Metabolic Syndromes

PGC-1α is a key coactivator in the regulation of metabolic function (43). Early work on PGC-1α revealed that this coactivator is expressed in muscle and brown adipose tissue in mice and is highly inducible by exercise, fasting, and cold exposure. It was revealed to be a coactivator for PPARγ (and for other NRs) when knocked out or ectopically expressed in mice, further reinforcing its role in metabolism (43–45). A polymorphism in the PGC-1α gene (G482S) and another polymorphism in the gene's promoter have been linked with an increased risk of type 2 diabetes (46–48), although these findings have not yet been generally accepted (49). A defect in the inducible expression of PGC-1α also has been linked to cholesterol cholelithiasis (gallstones) (50); this group also observed an increase in hypertension in carriers of a G482

TABLE 1. Survey of coregulator involvement in human diseases

Disease state or coregulator defect	No. of coregulators (out of 285)
Over- or underexpressed in cancer	101
Inflammation	5
Metabolic	2
Congenital syndrome	21
Fusion protein	6
Polymorphisms	12
Non-cancer	16
Coregulator	Disease state
Akt	Multiple cancers[1,2]
ARA55	Prostate cancer OE[3]
ARA70	Polycystic ovarian syndrome OE[4]
β-catenin	Dupuytren's disease and multiple cancers OE[5,6]
BRCA1	Breast, ovarian cancer[7]
BRCA2	Breast, ovarian, multiple cancers[7]
BRG1	Lung cancer OE, gastric, breast, and pancreatic cancer null/UE[8–11]
Calreticulin	Inflammatory bowel syndrome—autoantigen, Weldenstrom's macroglobulemia, multiple other diseases[12,13]
CARM1	Prostate cancer, homocysteine plasma regulation[14,15]
CAV1	Heart disease,[15] brachycardia, breast cancer OE, atherosclerosis[16,17]
CBP	Rubenstein-Taybi syndrome[18]
CDC-25B	Gliomas, esophageal squamous cell carcinomas[19,20]
CDK7	Alzheimer's disease, aging of the hippocampus[21]
CFL1	Breast cancer OE[22]
CITED1	Thyroid carcinomas OE[23]
CoAA	Lung, squamous cancer, and lymphomas gene amplification[24]
Cyclin A1	Acute myeloid leukemia, testicular cancer OE[25,26]
Cyclin A2	Gastric carcinoma, multiple cancers OE[27]
Cyclin D1	Breast cancer, multiple cancers OE[28–30]
Cyclin D3	Ta/T1 bladder cancer, colorectal, laryngeal squamous cell carcinomas, multiple myelomas OE[31–34]
Cyclin E1	Breast, bladder cancers OE[35–37]
DAP3	Thymoma OE, SNPs underlie asthma[38,39]
Daxx	Prostate stromal cancers OE[40]
DJ-1	Parkinson's disease[41–43]
DNAJB1	Role in hepatic B X protein turnover[44]
DRIP130	Nonmetastatic melanomas OE[45]
E6-AP	Angelman syndrome, breast, cancer prostate OE[46,47]
ELL	Leukemias OE[48,49]
FKHR	Alveolar rhabdomyosarcomas fusion protein[50]
Fli-1	Ewing sarcoma fusion protein,[51] fibrotic scleroderma[51,52]
FLNa	Frontomethphyseal dysplasia, otopalatodistal type I syndrome, West syndrome, Danlos syndrome, periventricular heterotopias[53,54]
Gelsolin	N187Y and G654A polymorphisms lead to amyloidosis, cardiac pathology, amyloid angiopathy[55–58]
HDAC3	Astrocyclic glial tumors OE[59]
HDAC4	Nonsyndromic oral clefts—germline mutations[60]
HMG-1	Sjogren's syndrome, proinflammatory cytokine pathology[61,62]
HMG-2	Systemic sclerosis[63]
JAB1	Oral squamous cell carcinoma[64]
Ku80	Autoantigen, Werner syndrome, melanomas, acute lymphoblastic leukemia, esophageal squamous cell carcinoma and breast cancers OE[65–67]
LATS2/KPM	Breast cancer and acute lymphoblastic leukemia[68–72]
MGMT	Gliomas OE[73,74]
MLL2	Leukemias, solid tumors[75,76]
MN1	Meningioma,[72] fusion protein MN1-TEL[77–79]
MTA1	Breast cancers possess splice variant, endometrial cancers OE[80]
MTA2	Ovarian cancers OE[81]
MUC1	Multiple cancers[82]
N-CoR	Colorectal carcinomas and endometrial cancers OE[83,84]
NSD1	Soto syndrome, familial gigantism[85,86]
p-TEFb	Multiple cancers[48]
p53	Multiple cancers, Li Fraumeni syndrome[87,88]
p54nrb	Splice variants in breast cancer, fusion protein in papillary renal cell carcinoma[89,90]
p57	Follicular lymphoma, non-small cell lung cancer, laryngeal cancers, pancreatic cancers, tetraploid hydropic placentas OE[91–95]
p68	Breast cancers OE[96]
p300	Rubenstein-Taybi syndrome, MOZ fusions, polymorphisms in intestinal and gastric tumors[97–99]
PAD4	Rheumatoid arthritis, adenocarcinomas OE[100,101]
PARP-1	Multiple cancers[102]

(*Continued*)

TABLE 1. *Continued*

Disease state or coregulator defect	No. of coregulators (out of 285)
PCAF	Colorectal and breast cancer OE, solid cancers[83,103,104]
PDEF	Prostate, breast, and ovarian cancer OE[105,106]
PDK1	Renal disease[107]
PGC-1α	Polymorphisms in diabetes (disputed), cholesterol cholelithiasis, metabolic syndrome in adolescents, Huntington's disease[108–114]
PGC-1β	Genetic variations correlate with obesity[115]
PELP1	Salivary gland duct adenocarcinomas, endometrial cancer OE[116–118]
PIAS1	Prostate cancer OE[119]
PIAS3	Alcoholic and HCV cirrhosis, multiple cancers OE[120–122]
PIAS4	Myelodysplasic syndrome[123]
PIN1	Alzheimer's disease; gastric, salivary, colorectal, hepatic, esophageal, prostate, and other cancers OE[124–129]
PPM1D	Neuroblastomas, breast and ovarian cancer OE, gene amplifications in cancer[130–133]
PRAME	Ovarian adenocarcinomas, acute myelogenous leukemias, childhood acute leukemias, neuroblastomas, NSC lung and pineal cancers OE[134,135]
PUS1	Myopathy, lactic acidosis, and congenital sideroblasic anemias, mitochondrial myopathy, and sideroblastic anemias[136–139]
RACK1	Alcohol addiction susceptibility due to polymorphism, bipolar disorder[140,141]
RAF1	Prostate and lung (disputed) cancer OE[142,143]
RANBP2	ALK fusions in inflammatory myofibroblastic tumors[144]
Rb	Multiple cancers[145]
REA	Breast cancer UE[146]
REGγ	Breast cancer UE, autoantigen, thyroid cancer OE[147,148]
SAF-A	Breast cancer OE[149]
SAP30	Basal cell carcinoma OE[150]
SENP1	Prostate cancer OE[151]
Six3	Holoprosencephaly[152–154]
SNURF	Testicular germ cell cancer OE, imprinting defect—linked to Angelman and Prader-Willi syndromes[155,156]
SRA	Ovarian tumors OE, breast cancer OE[157–159]
SRC-1	Prostate, breast, and gastric cancers OE[160–164]
SRC-2	MOZ-SRC-2 fusion proteins in acute myeloid leukemia, brain and breast cancer correlation with ER/PR expression[165–176]
SRC-3	Breast, pancreatic, ovarian, endometrial carcinoma, esophageal squamous cell carcinomas, colorectal carcinoma, oral squamous cell carcinomas OE, smaller isoform in breast cancer, gastric cancer, polymorphisms can protect against breast cancer and influence calcaneal bone density[177–217]
SRY	Oral squamous cell carcinomas OE, teratozoospermia, 46XX AIS, anorchia, myocardial infarction[218–220]
STAT3	Oral squamous cell carcinomas, ovarian and gastric cancers[221–225]
SUMO-1	Type II diabetes[226]
SYT	SYT-SSXZ fusion protein in synovial sarcomas[227,228]
TBL1	X-linked late-onset sensorineural deafness, polymorphisms, splicing errors[229]
TBP	Creutzfeldt Jakob syndrome susceptibility and other neurodegenerative diseases, diabetes, SCA17 syndrome due to poly Q tract variants[230–233]
TDG	Lung cancer susceptibility from polymorphisms, pancreatic cancer OE[234,235]
TGIF	Gastric cancer OE, sporadic holoprosencephaly[236,237]
TLS	Fusion protein with p300[238]
TRAP100	Breast cancers OE[239]
TRAP220	Epilepsy UE[240]
TRRAP	Pancreatic cancers OE[241]
TSG101	Genetic variants influence HIV-1 infection, acute myeloid leukemia, gastrointestinal stromal, cervical, breast, and prostate cancers OE[242–246]
UBC9	Melanoma, ovarian and lung cancers OE[247]
VAV3	Prostate cancers OE[248,249]
WSTF	Williams syndrome[250]

Superscript numbers indicate references listed in Supplemental References A (published as supplemental data on The Endocrine Society's Journals Online web site at http://edrv.endojournals.org). OE, Overexpressed; UE, underexpressed; HCV, hepatitis C virus; NSC, non-small cell carcinoma; ALK, anaplastic lymphoma kinase.

allele and suggested that it may be responsible for early-onset hypertension. The related protein PGC-1β has recently been knocked out in mice, revealing that it also is involved in metabolic functions. PGC-1$\beta^{-/-}$ mice have reduced mitochondrial function and other defects in fat metabolism (51, 52). PGC-1β can promote the formation of oxidative type IIX muscle fiber, which is an important issue in athletic performance (53).

Other coactivators also have been shown to be important regulators of metabolism (54). SRC-1 and SRC-2 have been found to play opposing roles in energy metabolism through mouse knockout studies. SRC-1$^{-/-}$ mice are prone to obesity due to decreased energy expenditure, whereas SRC-2$^{-/-}$ mice are leaner due to the reduced transcriptional capacity of PPARγ2, essential for adipoctye differentiation (55–57). In SRC-2$^{-/-}$ mice, a subsequent increase in PGC-1α/SRC-1

TABLE 2. Summary of coregulators over- and underexpressed in human cancers in the ONCOMINE expression profiling meta-analysis database

Cancer type	No. of overexpressed coregulators (out of 285)	No. of underexpressed coregulators (out of 285)
Brain	104	93
Breast	104	32
Leukemia	170	84
Liver	43	14
Lung	153	79
Lymphoma	142	113
Melanoma	40	8
Prostate	117	86
Renal	58	20
Sarcoma	67	100
Ovarian	45	8
Other	344[a]	147

All 285 coregulators identified in our survey were queried in the ONCOMINE database. Incidences of coregulators overexpressed or underexpressed with better than $P < 10^{-4}$ significance are shown.

[a] Number is greater than 285 because coregulators are tabulated from cancers in aggregate.

interaction occurs, enhancing the thermogenic actions of PGC-1α in brown adipose tissue. SRC-3 has been shown to be involved in metabolism by promoting the formation of white adipose tissue; SRC-3$^{-/-}$ mice possess decreased adipose tissue mass (58). It was determined that SRC-3 is able to enhance CAAT enhancer binding protein-β (C/EBPβ)-mediated transcription of PPARγ2, essential for progression of adipoctye differentiation. Other studies have revealed that PPARγ2-mediated transcription is subsequently dependent upon the mediator subunit TRAP220, indicating that coactivators play important roles in multiple steps throughout adipoctye differentiation (59). Additionally, coactivation of another key adipoctye differentiation-related transcription factor, C/EBPβ, also depends upon the SWI/SNF chromatin remodeling coactivator (60), further reinforcing the fact that coactivators are intermingled at multiple steps in the sequential process of adipoctye differentiation.

Corepressors are involved in the regulation of additional select aspects of metabolic function. Clinically, it has been known that the antipsychotic valproic acid can lead to weight gain (61, 62), an effect that may be a consequence of its ability to function as a histone deacetylase (HDAC) inhibitor. Here, HDAC1 and HDAC3 repress the transcriptional program of C/EBPβ and PPARγ, respectively, whereas their suppression by HDAC inhibitors allows for adipoctye differentiation to ensue unabated (63). Another important corepressor involved in metabolic regulation is receptor-interacting protein 140 (RIP140), which can repress the transcription of a variety of genes involved in fat and carbohydrate metabolism. Loss of RIP140 in knockout mice results in a lean phenotype, resistance to obesity, and increased insulin sensitivity (64).

The sirtuin HDACs (SIRT1–7) are involved in metabolic syndromes (65). Here, age- and diet-related metabolic issues are associated with loss of sirtuin HDAC activity and corresponding defects in glucose metabolism and mitochondrial function. Under conditions of restricted caloric intake, SIRT1 activity is enhanced in various tissues along with improvements in metabolic function and longevity (66). SIRT4 functions as an HDAC that directly targets mitochondria (67). SIRT6 is involved in the nuclear regulation of genes involved in metabolic physiology; it also contributes to genomic stability, and its loss leads to an aging-like phenotype (68). Given the significant structural differences in the sirtuin class of HDACs and their distinctly different enzymatic mechanism from non-sirtuin HDACs, this class of proteins represents promising targets for the design of new drugs to treat metabolic syndromes (69, 70). Indeed, resveratrol, a compound naturally existing in grapes (and red wine), can function as an SIRT1 activator and improves metabolic function in animals (71, 72).

VII. Heritable Syndromes

Germ-line coregulator gene disruptions are responsible for some inherited genetic syndromes. Mutations in E6-AP are responsible for Angelman syndrome, an imprinted heritable condition in which mutations on the maternal allele cause severe mental retardation and ataxia (73, 74). The Rubenstein-Taybi syndrome results from mutations in the CBP or p300 genes and leads to mental retardation and characteristic morphological defects (75, 76). It should be noted that for both the Angelman and Rubenstein-Taybi syndromes, carriers do not manifest clear defects that can be attributed to any specific NR, likely due to the pleiotropic actions of both of these coactivators. Other cases of heritable coactivator-related syndromes include Huntington's disease, where poly Q expansions in the Huntington (htt) gene disrupt PGC-1α function, resulting in deficient mitochondrial function in the striatum

TABLE 3. Selective pressure on coregulator alleles in three human population groups

Caucasian		African		Asian	
Coregulator	*P* value	Coregulator	*P* value	Coregulator	*P* value
GAC63	0.00145	SRC-1	0.000448	RANBP2	0.000741
SF3A1	0.00329	CAPER	0.00829	CAPER	0.00278
EDD	0.00742	Sin3A	0.00829	DAP3	0.00338
MIP224	0.0105	RTA	0.0218	MUC1	0.00408
ARIP3	0.0127	Rb	0.0219	JHDM2A	0.00686
CAPER	0.0127	NRIF3	0.0257	GAC63	0.00760
hZimp7	0.0127	p300	0.0258	PDK1	0.0141
MCRS1	0.0129	CBP	0.0258	ASC-2	0.0141
ASC-2	0.0228	CARM1	0.0313	PNRC	0.0207
Daxx	0.0415	GAC63	0.0314	TRIP12	0.0237

The 10 coregulator loci in three human population groups subject to the strongest positive selection pressure (having the most significant *P* values) are listed [see Voight *et al.*, 2006 (102)].

TABLE 4. Mouse coregulator knockouts

Coregulator	Knockout phenotype
AIB3	Defective placentation and embryonic lethality[1]
ARIP3/PIASx	Reduced testis weight[2]
β-catenin	Embryonic lethality at gastrulation[3]
Bcl-3	Immunological defects[4]
BRCA1	Embryonic lethality[5]
BRCA2	Embryonic lethality[5]
Brg1	Embryonic lethality,[6] zygotic genome activation,[7] neural stem cell maintenance and gliogenesis,[8] T cell development[9]
Calreticulin	Embryonic lethality, required for integrin-mediated calcium signaling and cell adhesion[10]
CARM1	Embryonic lethality[11,12]
Caveolin-1	Viable, but with lipid, muscle and pulmonary defects[13]
CBP	Dosage sensitivity, T cell developmental defect[14,15]
Cdc25	Absence of apparent phenotype[16,17]
CITED1	Aberrant pubertal mammary ductal morphogenesis[18]
CRABP-II	Postaxial polydactyly[19]
CtBP1	Small, viable and fertile[20]
CtBP2	Axial patterning defect, embryonic lethality[20]
CtIP	Early embryonic lethality, G1 defect, haploid insufficiency leads to tumor susceptibility[21,22]
Cyclin A1	Required for meiosis in male mice[23]
Cyclin A2	Early embryonic lethality[24]
Cyclin D1	Viable, reduced mammary gland carcinoma susceptibility[25]
Cyclin D3	Megaloblastic anemia, neurological abnormalities in ″D-x only knockout animals″[26]
Cyclin E1	Viable, resistance to oncogenic transformation[27]
Daxx	Embryonic lethality, extensive embryonic apoptosis[28]
DJ-1	Hypersensitivity to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrindine (MPTP) and oxidative stress[29]
DNAJA1	Defects in spermatogenesis[30]
DNAJB1	Defect in thermotolerance[31]
E6-AP	Gait ataxia, Purkinje neuron defect,[32] steroid hormone resistance, reproductive defects[33]
Edd	Needed for yolk sac vascularization and chorioallantoic fusion[34]
ELL/MEN	Embryonic lethality[35]
FHL2	Decreased bone mineral content, not needed for cardiac function/development[36,37]
FKHR	Incomplete vascular development, embryonic lethality[38]
Fln-A/filamin A	Cardiac malformations and midline skeletal defects[39]
FoxH1	Embryonic lethality, anterior-posterior patterning and node formation, specifies the anterior primitive streak[40,41]
GCN5	Embryonic lethality[42]
GCN5L2	Increased apoptosis and mesodermal defects in embryogenesis[43]
Gelsolin	Blocks podosome assembly, increased bone mass and strength[44]
HDAC4	Controls condrocyte hypertrophy during skeletogenesis[45]
Hey1	Embryonic lethality, required for vascular development[46]
Hmg1	Lethal hypoglycemia in neonatal mice[47]
Hmgb2	Reduced fertility, spermatogenesis defects[48]
Itchy	Immunological defect, skin inflammation[49]
Jab1	Early embryonic lethality[50]
Ku80	Hypersensitivity to DNA damage, growth retardation, V(D)J recombination defect[51,52]
LANP/pp32	No apparent phenotype[53]
Lats2/Kpm	Embryonic lethality, control of proliferation and genomic integrity[54]
Mat1	Early embryonic lethality, conditional ablation in Schwann cells yields viable cells[55]
MGMT	Increased tumorigenesis in the presence of methylnitrosourea[56]
Mll2	Embryonic lethality, multiple epigenetic-related defects[57]
Mn1	Defects in development of membranous bones of the cranial skeleton[58]
mSin3A	Embryonic lethality, T cell developmental defect[59]
Muc1	Impaired cholesterol uptake and absorption, decreased susceptibility to cholesterol gallstone formation[60,61]
PDK1	Embryonic lethality, cell size control, targeted deletion in heart leads to heart failure and increased sensitivity to hypoxia[62,63]
N-CoR	Embryonic lethality, erythrocyte, CNS and thymocyte developmental defects, defective astrocyte differentiation[64]
NSD1	Required for early postimplantation[65]
p53	Cancer susceptibility[66–68]
p57/KIP2	Skeletal abnormalities and growth retardation[69,70]
p120-catenin	Inflammatory responses in the skin, dendritic spine, and synapse development[71,72]
p300	Gene dosage-dependent embryonic development, proliferation defects, T cell development[73]
PARP-1	Hypersensitivity to ionizing radiation and DNA damaging chemicals, genomic instability[74]
PCAF	Viable, normal mice[42]
PGC-1α	Adaptive energy metabolism defect, CNS-linked hyperactivity, contractile function of cardiac muscle, regulation of hepatic heme biosynthesis, porphyria, heart failure susceptibility after transverse aortic constriction[75–83]
PIAS1	Defects in innate immunity[84]
PIMT	Fatal progressive epilepsy[85]
Pin1	Normal development, defect in entering cell cycle from G(0) arrest, resembles cyclin D1 null phenotype[86,87]
PRMT2	Required for early postimplantation in mouse development[88]

(*Continued*)

TABLE 4. *Continued*

Coregulator	Knockout phenotype
Prox1	Required for lymphatic system development[89]
PYK2	Macrophage morphology and migration[90]
RanBP2	Haploinsufficiency causes deficits in glucose metabolism[91]
Rb	Retinal development, multiple other disease states[92]
REA	Haploinsufficiency leads to increased uterine[93] and mammary gland responsiveness to estradiol[94]
REGγ	Growth retardation, immune defects[95,96]
RelA	Embryonic lethality, liver degeneration[97]
RNA Helicase A	Essential for gastrulation, early lethality[98]
Rig-1/Robo3	Required for midline crossing by hindbrain precerebellar neurons and axons[99]
RIP140	Ovulation defect, essential for female fertility, lean phenotype, adipoctye differentiation defect[100–102]
Sirt1	Small mice, retina and heart defects, rarely survive beyond parturition, involved in response to chronic genotoxic stress, gametogenesis, p53 hyperacetylation[103–105]
six3	Holoprosencephaly[106]
SMAD3	Impaired mucosal immunity, diminished T cell responsiveness to TGFb[107]
SRC-1	Moderate motor dysfunction, delayed development of Purkinje cells, control of energy balance, loss of skeletal response to estrogen, altered hypothalamic-pituitary-adrenal axis function, hepatic function[108–113]
SRC-2	Control of energy balance in white and brown adipose tissue, essential for progesterone-dependent uterine and mammary morphogenesis, testicular degeneration, spermatogenesis defect, placental hypoplasia[110,111,114–116]
SRC-3	Smaller animals, delayed puberty, reduced mammary gland development, reduced adipogenesis and inhibition of neointima formation by estrogen, lower response to IGF-I[117–120]
Stat3	Early embryonic lethality[121]
SUMO1	Haploinsufficiency leads to cleft lip and palate[122]
SYT/SS18	Early embryonic lethality, affects PPARBP expression[123]
TBP-1/PSMC3	Early embryonic lethality[124]
TGIF	Intragenic deletion of TGIF causes brain developmental defect,[125] other report indicates lack of holoprosencephalic defect in mice[126]
TIF1β	Embryonic lethality, early postimplanation development, required for maintenance of spermatogenesis[127–129]
TLS	Male sterility, radiation sensitivity[130]
TRAP100	Embryonic lethality, broad developmental role[131]
TRAP220	Embryonic lethality, needed for PPARγ2 stimulated adipogenesis, placental, cardiac, hepatic, and embryonic developmental defect[132]
Tsc2	Renal carcinogenesis, hepatic hemangiomatosis in happloinsufficient animals, embryonic lethality in null animals and unclosed neural tube[133]
TSG101	p53 accumulation, defective cell proliferation, early embryonic lethality[134]
UBA3	Cell cycle defects, embryonic lethality[135,136]
UbcH7	Placental defect and embryonic lethality (provirus disruption of gene in animal model)[137]
Vav3	Sympathetic hyperactivity, tachycardia and cardiovascular dysfunction[138]

Coregulator animal knockouts (whole animal disruption of coregulator genes) are shown. Coregulator knockout results in embryonic lethality in 53 of 92 knockout models. *Superscript numbers* indicate references listed in Supplemental References B (published as supplemental data on The Endocrine Society's Journals Online web site at http://edrv.endojournals.org). CNS, Central nervous system; PPARBP, PPAR-γ binding protein.

and subsequent neurodegeneration (77, 78). Also, an extension in a GAC repeat within the TRAP230 coactivator gene is associated with X-linked mental retardation and hypothyroidism (79). We predict that a larger number of less penetrant coregulator alleles waiting to be identified will affect a greater number of people, likely adding to the number of inherited coregulator disease syndromes.

Defects involving the ability of coregulators to properly interact with NRs can be clinically significant. The incomplete manifestation of the male phenotype due to androgen insensitivity syndrome (AIS) is another syndrome that can involve coregulators. Despite having the male 46XY chromosome arrangement, people with this syndrome possess an incomplete male (female-like) phenotype. AIS is most often due to mutations in the AR, impacting the ability of the receptor to bind androgens (80). Nevertheless, recent evidence points to the possibility that disruption in an AR coactivator also can be responsible for the AIS phenotype (81). In this case, a 46XY female AIS individual possessed a wild-type AR, and it was determined that the AF-1 of AR in this patient was unable to stimulate transcription of AR target genes, suggesting that a defect in an AR-specific coactivator may be responsible for this patient's phenotype. Also, some AR mutants found in AIS and prostate cancer patients lack the ability to properly interact with their coregulators. For instance, in one study, AIS (E2K) and prostate cancer AR (P340L) mutants interacted poorly with the AR corepressor ART-27, while still retaining the ability to interact with coactivators (82). A similar mechanism is responsible for resistance to thyroid hormone (RTH) syndrome, where mutations in TRβ that result in defects in corepressor dismissal and coactivator binding in the presence of thyroid hormone lead to RTH syndrome, despite normal hormone and DNA binding by the receptor. These patients often possess high circulating thyroid hormone levels, goiter, and other problems typically associated with hypothyroidism (83).

VIII. Coactivator Fusion Proteins

Fusions between the PML and retinoic acid receptor genes have long been recognized in cancer pathology where the ability of retinoids and HDAC inhibitors can effectively stop certain acute promyelocytic leukemias (84). Genetic disrup-

tions leading to coregulator fusions with other proteins exist in certain cancers. For instance, fusions of MOZ proteins with CBP, p300, and SRC-2 predispose to acute myeloid leukemia (85). SYT-SSXZ fusion proteins are responsible for synovial sarcomas (86), PAX3- and PAX7-FKHR fusion proteins lead to the formation of acute alveolar rhabdomyosarcomas (87), a TFE3-p54nrb fusion leads to papillary renal cell carcinomas (88), and RANBP2-ALK fusions result in inflammatory myofibroblastic tumors (89). The exact molecular mechanisms that underlie the carcinogenic actions of these fusion proteins likely stem either from their ability to interfere with the transcriptional program of transcription factors such as p53 and NRs or their ability to contradict the coregulator functions of their undisrupted coregulator counterparts (85).

IX. Coregulator Gene Polymorphisms

Coactivators function as "rheostats," controlling the extent of gene expression from NRs so that fluctuations in their expression or small changes in their biological activity will lead to significant differences in target tissue responses to hormone ligands. In human populations, the concentration of circulating steroid hormones falls within a fairly narrow range. Thus, alterations in the protein primary amino acid sequence and cellular concentration of coregulators may be responsible for individual differences in the manifestation of secondary sex traits, obesity, and susceptibility to cancer. Indeed, recent information argues that considerable variations in gene expression levels are present in different human populations and individuals, possibly in conjunction with specific polymorphic alleles (90). As we shall discuss in this section, coregulator gene polymorphisms exist in human population groups and could account for a subset of these phenotypic differences in NR ligands.

The majority of investigations have focused on the biological action of NR single nucleotide polymorphisms (SNPs) such as for TRβ (see *Section VI*) and more recently on ERα, PPARα, GR, and PR (91–94). Most coregulator SNPs are in coregulator gene promoters or intronic or synonymous noncoding variants (this is the case for other genes as well). Nevertheless, many SNPs exist within coregulator genes and affect coregulator amino acid sequence, such as for PGC-1α gene as discussed above. For SRC-3, 10 SNPs exist that affect the translated protein according to GenBank's dbSNP resource (95). One of these, a Q586H variant allele, confers a protective effect toward breast cancer (96). In this population-based study of German and Polish women, a clear correlation between this particular allele and the absence of breast cancer was seen in healthy women compared with cohorts with primary and recurrent breast cancer. In addition, other synonymous polymorphisms in the SRC-3 gene were revealed to confer a protective effect. Polymorphisms in PGC-1α, PGC-1β, and p300 were shown to be low-penetrance familial breast cancer markers (97), whereas another study indicates that p300 polymorphisms are linked to intestinal and gastric tumors (98).

The recent release of data from the international human HapMap consortium has identified approximately 6.3 million SNPs in four human population groups (99), and many of these SNPs reside within coactivator genes. Considerable effort is being directed toward understanding how SNPs (and other genetic variations) influence human disease susceptibility (100, 101). In a bioinformatic approach used to analyze positive selection pressures for particular alleles in four different ethnic groups using data from the international HapMap project, SRC-1 (NCOA1) is predicted to be under very strong selective pressure (the greatest for any human gene) in a Nigerian cohort (102). We also examined coregulators in our Nuclear Receptor Signaling Atlas (NURSA) coregulator list using a web resource developed by these authors (http://hg-wen.uchicago.edu/selection/haplotter.htm). This predicts that strong selective pressures exist for a number of coregulator genes that are listed in Table 3. Among coregulators, GAC63 (103) and RANBP2 (104) are under the strongest apparent selective pressures in Caucasians and Asians, respectively (Table 3). Thus many coregulators are predicted to be strong conduits for human evolutionary adaptation and may have arisen due to ethnic and migratory differences in diet or other environmental factors. However, in the context of our modern lifestyle and diet, these coregulator adaptations are likely to affect us in different and perhaps adverse ways.

X. Coregulator Knockout Studies

Considering the entangling issues of coregulator pleiotropy, knockout models provide a satisfying way to understand their physiological impact at the organismal level. In this regard, we are blessed with an abundance of such models; we have been able to identify whole-mouse knockout models for 92 coregulators in the literature (Table 4). Of these 92 knockout models, 53 die during embryogenesis, whereas a wide spectrum of phenotypes were observed for the others. The fact that over half of the coregulator knockouts we listed display embryonic lethality highlights the overall importance of coregulators in developmental biology. In humans, complete loss of these coregulators would be very rare, given the powerful selection pressure to drive out very deleterious alleles. However, we predict that many hypomorphic alleles for these same coregulators exist in human individuals that have yet to be linked to human disease. Also, coregulator knockout mice that are viable often display a spectrum of phenotypes and provide an impetus to relate them to human diseases that resemble the physiological defects observed in these model animals.

Knockout models for SRC-1 (105), SRC-2 (106), and SRC-3 (107, 108) have revealed a great deal about coregulator biology in a whole animal context. These knockouts possess a range of phenotypic defects, consistent with our assertions that coregulator pleiotropy influences a wide range of biological systems. These include reproductive (uterine and mammary gland) and metabolic (hepatic and adipoctye biology) defects (109) consistent with our understanding of their biological actions *in vitro*. Disruption of the p300 and CBP genes also affects mouse biology. Haploinsufficiency in either gene results in observable phenotypes resembling Rubenstein Taybi syndrome, whereas homozygosity or transheterozygosity ($p300^{+/-}$; $CBP^{+/-}$) results in embryonic le-

thality (110). N-CoR$^{-/-}$ animals also die during embryogenesis with defects in erythrocyte and thymocyte production and central nervous system defects including loss of astrocyte differentiation (111). Knockout of the PGC-1α gene reaffirms its role in metabolism (see *Section VI*). In an unanticipated way, though, this knockout animal revealed that PGC-1α can influence metabolic control through its actions in the central nervous system (112). Because it is impractical to discuss the whole litany of coactivator knockout studies listed in Table 4, we let this summary speak for itself. Coactivator proteins are vitally important for normal physiological function.

XI. Concluding Remarks

Herein, we have demonstrated that a preponderance of evidence exists in the literature and other sources that broadly link coregulators to a diverse array of human diseases. From this review, the following points can be made: 1) coregulators are a large protein group (including some RNA members; steroid receptor RNA activator); 2) coregulator dysfunction is not restricted to rare genetic conditions or a small subset of cancers, but is instead involved in numerous human diseases; 3) numerous mouse knockout studies attest to the physiological and pathological importance of coregulators; 4) coregulators are frequently over- or underexpressed in a wide range of cancers; and 5) human genetic variations are widely present in coregulator genes and are likely responsible for select human phenotypic variations in steroid biology, cancer, and metabolic disorders. As seen here, existing basic and translational research efforts have already shed some light on the relationship between coregulators and human diseases, yet we predict much more is to come. It is likely that the high association of coregulator misexpression with certain pathologies simply represents the results of the diseases where investigators have initially looked, and that in time, numerous associations with other diseases will be revealed. Developing genomic and proteomic technologies will add greatly to our understanding of the basic roles that these master regulators play at multiple levels, from the control of gene expression up to that of the whole organism. Overall, efforts that can integrate our basic and translational understanding of coregulators should lead to solutions for unmet medical needs of a wide range of human diseases.

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