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Receptor Coactivators: Master Regulators of Human Health and Disease

Subhamoy Dasgupta, David M. Lonard, and Bert W. O'Malley

Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas 77030

Bert W. O'Malley: berto@bcm.edu

Abstract

Transcriptional coregulators (coactivators and corepressors) have emerged as the principal modulators of the functions of nuclear receptors and other transcription factors. During the decade since the discovery of steroid receptor coactivator-1 (SRC-1), the first authentic coregulator, more than 400 coregulators have been identified and characterized, and deciphering their function has contributed significantly to our understanding of their role in human physiology. Deregulated expression of coregulators has been implicated in diverse disease states and related pathologies. The advancement of molecular technologies has enabled us to better characterize the molecular associations of the SRC family of coactivators with other protein complexes in the context of gene regulation. These continuing discoveries not only expand our knowledge of the roles of coactivators in various human diseases but allow us to discover novel coactivator-targeting strategies for therapeutic intervention in these diseases.

Keywords

coregulators; transcriptional cofactors; metabolism; cancer; reproduction

INTRODUCTION

Transcriptional coregulators have emerged as the principal regulators of gene expression by directly interacting with and modulating the activity of essentially all nuclear receptors (NRs) and transcription factors. On the basis of their functional output, coregulators can be classified into two major classes: coactivators, which are associated with agonist-bound NRs to induce gene expression, and corepressors, which selectively repress gene expression through interaction with unliganded or antagonist-bound NRs (1, 2). Transcriptional induction is an ordered and dynamic process in which a NR first receives a signal from its cognate ligand and then translocates to specific DNA sequences in the promoter region of a target gene (3). This is followed by the recruitment of coactivator complexes, which then mediate enzymatic reactions, remodeling the chromatin and facilitating the association of

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the RNA polymerase II complex with the general transcriptional machinery at the target gene promoter. Because coregulators influence the transcriptional activity of numerous NRs and other types of transcription factors, they exert broad genome-wide effects on genetic networks and contribute significantly to a vast spectrum of physiological abnormalities and diseases (Figure 1) (4).

Since the discovery of steroid receptor coactivator-1 (SRC-1) a decade ago (5), more than 400 coregulators have been identified, and deciphering their function has significantly contributed to our understanding of coactivator biology. Gene-deletion studies in mice have demonstrated distinct roles for individual coregulators in growth and development and associated pathological states in genetic, reproductive, and metabolic disorders and cancer (Figure 2) (6). SRC family members of the p160 class of coactivators have been widely implicated in the regulation of steroid hormone action by mediating functions of a majority of the NRs and transcription factors, and their aberrant expression in different malignancies and genetic diseases has distinguished them as master regulators of human pathologies (7). Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC-1 α) is another critical coregulator, which is involved in the regulation of metabolism and energy homeostasis. Expression levels of PGC-1 α in various tissues have been associated with genetic predispositions to diseases with impaired mitochondrial function, including type 2 diabetes mellitus and obesity (8). Other coactivators, such as CREB-binding protein (CBP)-p300, interact with virtually all transcription factors and regulate gene expression by relaxing chromatin structure at the target gene promoter through their intrinsic histone acetyltransferase (HAT) activity. Mutations in the CBP gene are linked to Rubinstein-Taybi syndrome, in which a deficiency of CBP HAT activity results in defective development and long-term memory formation (9). In addition to chromatin remodeling, coactivator-associated arginine methyltransferases (CARM1/PRMT4) also stimulate gene transcription by activation of NRs and other transcription factors in combination with the SRC family of coactivators (10). Thus, advances in coactivator biology have significantly enhanced our basic understanding of the underlying molecular causes of various human diseases, and this understanding can now be translated to the clinic through the discovery of novel coactivator-targeting therapeutics. This review outlines recent advances in coactivator biology and their implications in human health and disease, focusing primarily on SRC family members.

STRUCTURAL AND FUNCTIONAL DETERMINANTS OF SRC FAMILY MEMBERS

SRCs were the first of the gene families to be classified and characterized as coactivators for NRs. The SRC family consists of three members: SRC-1 (also known as NCOA1), SRC-2 (also known as NCOA2, GRIP1, and TIF2) and SRC-3 (also known as NCOA3, ACTR, AIB1, p/CIP, RAC3, and TRAM-1). The three members of the SRC family contain homologous domains and share sequence similarity—54% similarity between SRC-1 and -2, 50% between SRC-1 and -3, and 55% between SRC-2 and -3 (11, 12). Each member of the SRC family can enhance transcriptional activity of NRs by acting as a bridging molecule, assisting protein-protein interactions between NRs and multiple other coregulators and

facilitating the assembly of the transcriptome complex at the target gene promoter. SRCs contain three distinct structural domains. These include the N-terminal basic helix-loop-helix-Per/ARNT/Sim (b-HLH-PAS); the central NR interacting domain, containing three LXXLL motifs (where X is any amino acid); and two C-terminal activation domains, AD1 and AD2. The N-terminal b-HLH-PAS domain contains the most conserved motif among SRC family members. It can interact with several transcription factors, such as STAT6, TEF4, and p53, and with additional coregulators, such as coiled-coil coactivator (CoCoA), flightless-I (Fli-I), and Pin1, to activate transcription (13). Additionally, the b-HLH-PAS domain possesses a bipartite nuclear localization signal (NLS), and a NLS-mutant coactivator fails to localize to the nucleus and is insensitive to proteasome-dependent turnover, an important means to limit its transcriptional activity (14). The central three LXXLL motifs that form the amphipathic alpha-helices are responsible for direct interaction and binding to the ligand-binding domain of NRs. The LXXLL motif of the coactivators fits into the hydrophobic cleft in the ligand-binding domain of the ligand-bound NR, and this association is facilitated by adjacent amino acid sequences. The C-terminal activation domains AD1 and AD2 are responsible for recruiting several additional coregulators for chromatin remodeling of the gene promoter to potentiate active transcription (15). SRCs recruit chromatin-modifying enzymes such as CBP and HAT by directly interacting with the AD1 domain, whereas AD2 binds to several important histone methyltransferases such as CARM1 and Protein arginine N-methyl transferase 1 (PRMT1). In addition to their functions as adaptor molecules for recruiting several chromatin-modifying enzymes to the DNA promoter, SRCs have weak intrinsic HAT activity at the C-terminal domain (16). These different structural features make SRCs critical and diverse platforms for the assembly and coordination of a variety of coregulators and transcription factors at the gene promoter and for the modulation of NR-dependent transcriptional activity.

POSTTRANSLATIONAL MODIFICATIONS

Although SRCs initially were identified as bona fide coactivators for NR-dependent transcription, they also interact with many different transcription factors and potentiate their transcriptional activity. These include nuclear factor- κ B (NF- κ B), E2F1, Smads, hypoxia inducible factor 1 (HIF1), p53, signal transducers and activators of transcription (STATs), the ETS (E-twenty-six) family, and HNF4 (hepatocyte nuclear factor-4) (15). Recent advances in proteomic applications identified several factors associated with an endogenous coactivator complexome that includes building blocks, functional blocks, and regulatory subunits (17). Associations of these protein complexes are highly ordered processes that are regulated by SRCs in response to a variety of upstream extracellular stimuli to orchestrate selective upregulation of target genes. These precise genetic regulations by SRCs in response to signaling inputs are controlled by enzymes that impose posttranslational modification (PTM) codes on the coactivators. Different combinatorial PTM codes on SRCs alter their structural conformation and affinity toward specific transcription-complex proteins, promoting upstream-signal-specific genetic changes to execute physiological programs. The diverse sets of enzymes that interact with and modify SRCs include kinases, phosphatases, small ubiquitin-related modifier (SUMO) ligases, ubiquitin ligases, HATs, and histone methyl-transferases (18). Several extracellular stimuli such as steroid hormones,

growth factors such as epidermal growth factor (EGF) and heregulin, and cytokines transduce downstream signaling events, generating phosphorylation codes on SRCs. Particularly, mitogen-activated protein kinase (MAPK) phosphorylates SRC-1 at Thr¹¹⁷⁹ and Ser¹¹⁸⁵ and SRC-2 at Ser⁷³⁶, increasing coactivator affinity toward the androgen receptor (AR), estrogen receptor- α (ER α), and progesterone receptor (PR). Phospho-coded SRCs also have higher binding affinity for p300 and CBP, thereby enhancing their recruitment to the chromatin and activating NR-dependent transcription in a ligand-independent manner. Protein kinase A (PKA) has been documented to phosphorylate SRC-2, increasing its turnover and nuclear translocation, followed by rapid degradation by the ubiquitin-proteasome pathway (19).

Recent studies from our laboratory identified SRC-2 as a direct substrate of AMP-activated protein kinase (AMPK), and AMPK α 2-subunit-dependent phosphorylation of SRC-2 enhances the activity of transcription factor farnesoid X receptor (FXR) on target gene promoters (20). Among the SRC family members, SRC-3 is the most attractive substrate for multiple kinases, and the functional importance of these modifications in transcriptome assembly and coactivator biology has been extensively studied. Work from our laboratory and others has identified several sites (Thr²⁴, Ser⁵⁰⁵, Ser⁵⁴³, Ser⁶⁰¹, Ser⁸⁵⁷, Ser⁸⁶⁰, and Ser⁸⁶⁷) in the Ser-Thr-rich region of SRC-3 that are frequently phosphorylated by multiple kinases such as MAPK, inhibitor of kappa B kinase (IKK), protein kinase C ζ (PKC ζ), Akt, focal adhesion kinase (FAK), casein kinase 1 isoform δ , and extracellular-signal regulated kinase 3 (ERK3) (21–28). Phosphorylation of SRC-3 selectively increases its affinity for certain transcription factors and NRs, thereby potentiating robust transcriptional activity on target gene promoters. In addition to Ser-Thr kinases, the tyrosine kinase ABL phosphorylates SRC-3 on Tyr¹³⁵⁷, and this modification promotes rapid recruitment of p300 and CBP along with strong coactivation of NRs and NF κ B (29). These findings illustrate how PTM codes on SRC-3 allow it to accept signals from multiple pathways and to delicately coordinate biological functions by modulating specific genetic changes.

Combinations of PTM codes on SRC-3 further alter the nature and stability of the coactivator and supplement additional parameters that regulate its activity. Phosphorylation-dependent ubiquitination and regulation of SRC-3 protein turnover have identified intricately regulated combinations of PTM codes that modulate coactivator function. On one hand, phosphorylation of SRC-3 by glycogen synthase kinase 3 (GSK3 β) increases transcriptional activity by promoting subsequent coactivator degradation by ubiquitination, while on the other hand PKC ζ -mediated SRC-3 phosphorylation blocks its ubiquitination and increases its levels by hindering its proteasome-mediated degradation (30). In addition to ubiquitination, certain SRC family members are direct targets of SUMO ligases, and this modification sometimes competes with ubiquitinylation for the same lysine residue, which can alter the cellular fate of SRCs by blocking protein degradation while diminishing its transcriptional activity (15). Thus, combinatorial PTM codes on SRC-3 determine the coactivator concentration and the gene-selective potency that allows it to control signal-specific gene expression.

The activities of several coactivators other than SRC family members are regulated by PTMs. For instance, phosphorylation of a conserved Ser²¹⁷ residue in CARM1 functions as

a molecular switch leading to CARM1 activation (16). Additionally, an automethylation domain has been identified in CARM1, and this self-regulatory mark modulates CARM1-activated transcription and pre-mRNA splicing without affecting its enzymatic activity (31).

THE ROLE OF NUCLEAR RECEPTOR COACTIVATORS IN HUMAN DISEASE AND PATHOLOGY

Many of the functions of coactivators, particularly of the SRC family members, that we understand today were discovered in classical mouse genetic studies that demonstrate exclusive roles for each SRC in reproduction, cancer, and metabolic homeostasis.

Reproductive Functions

SRCs are dominant coactivators involved in reproductive physiology regulating uterine growth, embryo implantation, and fertility. Disruption of the SRC-1 gene in mice resulted in decreased growth and development of reproductive organs without eliminating viability and fertility. Loss of the SRC-1 gene significantly reduced uterine, prostatic, testicular, and mammary gland growth in response to steroid hormone stimulation. SRC-1 ablation decreased uterine growth by 60% and is recognized as the most potent coactivator for ER- and PR-dependent functions in the uterus (32). In contrast, SRC-3 is the primary coactivator for ER and PR in mammary luminal epithelial cells (33, 34). Additionally, SRC-3 knockout mice exhibit pleiotropic processes including postnatal growth retardation, delayed puberty, abnormal reproductive physiology, and reduced mammary-ductal branching and alveologenesis (34). SRC-2 gene global knockouts show striking abnormalities in reproductive functions of both sexes. Male SRC-2 knockouts are hypofertile owing to defects in spermatogenesis and testicular degeneration, whereas female hypofertility is attributed to placental hypoplasia, a block in embryo implantation, and a defective decidual response (35). In addition, loss of the SRC-2 gene in PR^{Cre/+} bigenic mice resulted in reduced mammary-ductal side branching and alveologenesis, suggesting an essential role for SRC-2 in progesterone-induced mammary morphogenesis (36). Although single-knockout mice for each SRC family member are viable, the phenotypes observed in double-knockout mice are lethal. This indicates a degree of physiological cooperation among SRC family members compensating in part for defects in the functional output.

In humans, SRCs are altered in endometriosis, a disease in which cells from the lining of the uterus during retrograde menses survive and grow outside the abdominal cavity. Although immunohistochemical analysis demonstrated endometriotic tissue-specific expression of all SRCs, full-length SRC-1 is expressed at lower levels than in normal endometrium (37). Recent studies from our laboratory uncovered a novel signaling axis involving SRC-1 in an endometriosis mouse model and biopsied stromal cells from human patients. We identified reduced expression of full-length SRC-1 in eutopic and ectopic endometrium of mice with a concomitant increase in a 70-kD SRC-1 proteolytic isoform compared to normal endometrium. Mechanistic studies revealed that tumor necrosis factor α (TNF α)-mediated matrix metalloproteinase-9 (MMP-9) activation cleaves full-length SRC-1 to generate the 70-kD isoform, which in turn blocks TNF α -induced apoptosis and promotes cellular invasion and epithelial-mesenchymal transition (EMT) (38). This newly discovered SRC-1

isoform has strong clinical implications for endometriosis patients and potentially can be used for diagnostic and therapeutic purposes (39). Other ER coactivators have been implicated as a risk factor for endometrial cancer. Studies have identified cumulative genetic variations of the SRC-2 cofactor complexosome as a whole, including SRC-2, CARM1, p300, CBP, and PRMT1, as a significant risk associated with endometrial cancer (40).

Energy Metabolism

NR coactivators also have emerged as primary regulators of metabolic homeostasis in different tissues. Global-knockout mouse models deleting each SRC family member, as well as tissue-specific deletion of SRCs, have identified important metabolic pathways that they regulate. Understanding these pathways has broadened our knowledge of the molecular mechanisms of metabolic disorders such as diabetes, obesity, and certain genetic disorders. For instance, whereas SRC-1^{-/-} mice are prone to obesity owing to decreased energy expenditure, SRC-2^{-/-} mice are protected from high-fat-induced obesity, suggesting a dynamic interplay of the coactivators regulating normal metabolic physiology (41). SRC-2 knockout mice display increased insulin sensitivity, higher lipolysis, and decreased fat uptake in conjunction with enhanced adaptive thermogenesis by modulating brown adipose tissue (BAT) activity. Molecularly, loss of SRC-2 decreases peroxisome proliferator-activated receptor (PPAR) activity in white adipose tissue (WAT), whereas it induces interaction of SRC-1 with PGC1 α in BAT, thereby promoting thermogenic activity. In part, these mechanisms address the obesity-resistant phenotype observed in SRC-2^{-/-} mice (41). In addition to the roles of SRC-1 and SRC-2 in energy metabolism, SRC-3 is an important coordinator of white adipocyte development, and SRC-3^{-/-} mice show impaired adipocyte formation (42, 43). Mechanistically, SRC-3 coactivates transcription factor CAAT/enhancer-binding protein to induce expression of PPAR γ 2, promoting adipogenesis. Loss of SRC-3 thus impairs the white adipogenic program (44). Similarly, SRC-1/SRC-3 double-knockout animals exhibit defective adaptive thermogenesis and low BAT activity due to downregulation of selective PPAR γ target genes. These animals are lean compared to their wildtype littermates and are resistant to diet-induced obesity (45). Collectively, SRC family members have emerged as gatekeepers of energy homeostasis, maintaining the balance between BAT and WAT.

In addition to their distinct roles in adipogenesis, SRC family members display important phenotypic effects in muscle and liver energy metabolism. Global metabolomic profiling of SRC knockout animals identified common metabolites that are statistically altered in different SRC family members (46). Interestingly, SRC-3 knockout mice display an increase in long-chain acyl carnitine in skeletal muscle due to reduced expression of the long-chain fatty acid transporter carnitine/acylcarnitine translocase (CACT). As a result of this genetic discrepancy, SRC-3^{-/-} mice resemble the CACT-deficiency phenotype observed in humans, characterized by a syndrome of hypoketonemia, hypoglycemia, hyperammonemia, and impaired neurologic, cardiac, and skeletal muscle performance (46). Targeted deletion of SRC-2 in skeletal muscle increases mitochondrial uncoupling in muscle myocytes by modulating the expression of the UCP3 gene with a simultaneous increase in energy expenditure, thus delaying the development of type 2 diabetes (47). CARM1 plays a pivotal role in myogenesis and muscle differentiation in conjunction with SRC-2. CARM1

physically interacts with SRC-2 and is responsible for the recruitment and activation of the MEF2 transcription factor on the creatine kinase promoter. Inhibition of CARM1 significantly abrogates muscle differentiation and decreases expression of the important muscle transcription factors myogenin and MEF2 (48). Metabolically, CARM1 is associated with muscle glycogen synthesis by directly regulating transcription of *Gys1* (glycogen synthase 1), *Pgam2* (muscle phosphoglycerate mutase 2), and *Pygm* (muscle glycogen phosphorylase) genes. Attenuation of CARM1 significantly reduces muscle mass, suggesting it plays a role in human glycogen-storage diseases (49).

Loss of SRC-2 also affects hepatic glucose release owing to reduced expression of glucose-6-phosphatase (G6Pase). As a result of this genetic defect, SRC-2^{-/-} mice show fasting hypoglycemia and resemble the phenotype observed in human glycogen-storage disorder-1a (Von Gierke's disease). Molecularly, SRC-2 strongly coactivates the orphan NR RORα on the G6Pase promoter to regulate G6Pase transcription and hepatic glucose release (50). SRC-1^{-/-} mice exhibit a hypoglycemic condition in both fasting and fed states, and this is partly due to impairment of the gluconeogenic program. SRC-1 directly coordinates rate-limiting enzymes of the gluconeogenic pathway such as pyruvate carboxylase, phosphoenolpyruvate carboxykinase (PEPCK), and fructose-1, 6-bisphosphatase (FBP1), thus restoring normal glucose levels in fasting conditions (51).

Recent findings from our laboratory also identified SRC-2 as an essential coordinator of whole-body energy homeostasis. It acts by regulating the absorption of dietary fat and energy utilization. Reduced energy status activates the fuel-sensor kinase AMPK, which then phosphorylates and activates SRC-2. Activated SRC-2 stimulates the action of the FXR transcription factor on the bile salt export pump (BSEP) promoter, thereby increasing its gene transcription. BSEP causes secretion of bile acid, allowing absorption of dietary fats and triglycerides, which are then circulated to various organs for restoration of energy. As expected, both global SRC-2 knockout mice and liver-specific SRC-2 deletion phenocopies increased fecal triglycerides and decreased plasma triglycerides, suggesting that loss of SRC-2 attenuates absorption of dietary fats (20). Based on these observations, it is reasonable to speculate that the AMPK-SRC-2 axis serves as a potential therapeutic target to modulate whole-body energy homeostasis (52). Ablation of SRC-2 also affects the metabolic program in the adult heart with impaired sarcomeric gene expression, mimicking a stressed heart phenotype. These studies conclude that SRC-2 acts as a pivotal transcriptional regulator in the adult heart and that it is required for normal functioning during pressure overload (53). Recent studies from SRC-1 and SRC-3 double-knockout mice found that the dual loss of these coactivators enables resistance to age-related obesity and glucose intolerance by the upregulation of insulin receptor substrate 1 (IRS1) (54). Taken together, these findings emphasize the importance of SRCs as essential coordinators of energy metabolism and highlight their clinical implications in various metabolic and genetic disorders.

Cancer Progression and Metastasis

Each member of the SRC family is overexpressed and/or amplified in different types of cancers (reviewed in Reference 15). In particular, SRCs have been widely implicated in

endocrine-related cancers such as breast, prostate, endometrial, and ovarian cancers. In breast cancer, SRC-3 and SRC-1 genes are frequently amplified and/or overexpressed, and their expression positively correlates with poor prognosis and more advanced disease stage. Molecularly, SRC-1 promotes breast-to-lung metastasis by upregulating Twist expression and coactivating the polyoma enhancer activator 3 (PEA3) transcription factor, thereby promoting migration, invasion and EMT (55). In addition to its established role in tamoxifen-resistant breast cancer, SRC-1 has been implicated in aromatase inhibitor (AI)-resistant recurrent breast cancer (56). Resistant patients exhibit increased expression of SRC-1, which correlates with poor disease-free survival and distant organ metastasis. This is achieved partly by direct interactions with the ETS2 transcription factor and induction of the downstream target genes *MYC* and *MMP9*, which are responsible for the invasive and migratory phenotypes seen in AI-resistant breast cancer cells (56). Thus, SRC-1 has been proposed to be a dynamic coactivator that can switch breast tumor progression from a steroid-responsive to a steroid-resistant state. SRC-1 transcriptionally enhances a critical protease, ADAM22, responsible for aggressive phenotypes in breast cancer cells independent of ER. Also, integrin- α (5) (ITGA5) is a direct target of SRC-1 in ER-negative breast tumors; it controls a cascade of downstream signals regulating cell adhesion (57). These findings vividly demonstrate that SRC-1 can promote aggressive breast tumor phenotype and suggest that therapeutic intervention targeting SRC-1 should be advantageous to breast cancer patients.

SRC-3 has been extensively studied in various breast cancer mouse models because of its crucial role in tumor growth, cellular proliferation, EMT, and invasiveness (15). Importantly, SRC-3 serves as a downstream master effector molecule of the Her-2 signaling axis, and loss of SRC-3 significantly attenuates Her-2-dependent breast tumor progression (58). Multiple kinases tend to modulate SRC-3 activity through various PTM codes, demonstrating the global role of SRC-3 in integrating upstream signaling events to promote aggressive progression in breast cancer. In addition to ER and PR, SRC-3 functionally activates other breast oncogenic transcription factors such as NF κ B, PEA3, and IKK, and facilitates transcriptional upregulation of cancer-specific genes (21, 22, 27). Common downstream targets affected by SRC-3 activation include the insulin-like growth factor-1 (IGF1) pathway, cyclin D1, and MMPs (15). Recent studies have identified a novel cofactor, PELP1, which plays an important role in ER α signaling by directly interacting with CARM1. PELP1 is a proto-oncogene aberrantly expressed in breast cancer, and its interaction with CARM1 synergistically enhances ER α transactivation. Interestingly, PELP1 and CARM1 were found to be co-overexpressed in a subset of ER-positive breast cancers and were suggested as attractive therapeutic targets (59). CARM1 has also been identified to be a dominant coactivator in a variety of cancers, including colon cancer, where it was found to coactivate β -catenin downstream of Wnt signaling. Depletion of CARM1 significantly reduced Wnt-induced target gene expression, thereby suppressing tumor cell growth and survival (60).

SRC-3 has been implicated in other cancers as well. Recent evidence suggests increased copy-number alteration of SRC-3 in a subset of lung cancers (61). Studies from our laboratory identified SRC-3 to be a substrate of an atypical MAPK named ERK3, which

signals SRC-3 to promote invasion-metastasis by enhancing expression of MMP genes in lung cancer cells (27). In prostate cancer, SRC-2 has been identified as a dominant oncogene amplified in ~8% of primary tumors and ~37% of metastatic patients (62). SRC-2 acts as a strong coactivator of AR, and promotes prostate cancer cell growth by activating cyclin D1 gene expression (63, 64). In addition, SRC-2 has AR-independent functions and can promote prostate cancer cell growth in the absence of AR. SRC-2 expression positively correlates with aggressive prostate cancer in patients, and its expression is a valuable indicator of time to disease recurrence (64). Several SRC-2 mutations have been identified in lung cancer, prostate cancer, and melanoma. The majority of these mutations (G435S, G439D, and P470S) have been identified in the Ser/Thr-rich domain, which is a direct target of several kinases (62). One of these mutations lies in the AD1 region responsible for recruitment of p300 and CBP; however, the functional significance of these mutations with respect to disease progression remains unknown. In prostate cancer, the cofactor PGC-1 α also has been reported to be a strong coactivator of AR by directly interacting with the transactivation domain of AR. Depletion of PGC-1 α significantly decreased AR-dependent prostate cancer cell growth by inducing a cell cycle G1 arrest, suggesting that PGC-1 α could be a potential target for prostate cancer therapy (65). In a subset of acute myeloid leukemia (AML) patients, SRC-2 gene fusions with monocytic leukemia zinc finger protein (MOZ) have been detected (66). A gene rearrangement occurs between the 5' of the MOZ gene and the 3' of the SRC-2 gene, encoding the transcriptional activation domain of MOZ and the coactivator AD1 domain. This rearrangement enables the expressed fusion protein to recruit CBP, which drives AML (67). Recent findings also identified *SRC-1* as a potential driver gene in chromosome 2p that is frequently found to be amplified in chronic lymphocytic leukemia (CLL). Gain of 2p chromosomal region function in CLL patients is detected at an early stage of the disease and correlates with poor prognosis, indicating SRC-1 may contribute to the pathological state of CLL (68). A recent study identified enhanced expression of the PGC-1 α coactivator in a subset of human melanoma tumors. PGC-1 α -positive melanoma cells exhibited increased mitochondrial activity and were resistant to reactive oxygen species stress (69).

In addition to the involvement of SRCs in cancer (70), recent evidence points to a requirement for coactivators in chemoresistance (71) as well as in stem cell self-renewal and pluripotency maintenance (72, 73). Under cytotoxic stress, SRC-3 deregulates p53 induction by upregulating TNF receptor-associated factor 4 (TRAF4), which competes with p53 for binding to the deubiquitinase HAUSP (herpesvirus-associated ubiquitin-specific protease). This ability of SRC-3 along with TRAF4 to destabilize p53 may be an important mechanism for chemoresistance to current breast cancer therapies. SRC-3 was also found to directly bind to the estrogen-related receptor β (Esrrb) and promote Esrrb transcriptional activity by recruiting CBP and CARM1 to regulate *Oct4*, *Sox2*, and the *Nanog* gene network (73). ChIPseq studies identified an overlapping regulatory network of SRC-3 with Esrrb supporting the Oct4-Sox2-Nanog transcriptional program to maintain embryonic stem cell (ESC) pluripotency and self-renewal (72). These studies propose a new concept in stem cell biology and suggest a dynamic interplay involving the SRC coactivators and the transcription factors in ESC maintenance. It will be interesting to decode other possible coactivator functions in cancer stem cell biology.

TARGETING STRATEGIES

Because the coactivators can integrate numerous upstream signaling events into functional outputs, they may be an attractive therapeutic target for the treatment of cancer. As opposed to NRs, which are relatively easy to target thanks to their affinity for ligands, coactivators are more difficult to target with small molecules (6). Approaches to block coactivator molecules include targeting the enzymes that posttranslationally modify the coactivators, thereby altering the stability of the proteins (74). However, recent high-throughput screening has identified small-molecule inhibitors that can target SRC-1 and SRC-3 by direct binding to these coactivators (75). Binding of small-molecule inhibitors to the oncogenic SRC-3 coactivator promotes its degradation and attenuates cancer cell growth. This proof-of-principle study laid the foundation for an ongoing screening effort.

CONCLUSION

Transcriptional coactivators have emerged as “master regulators” of human physiology, and their dysregulation has been implicated in numerous diseases (76). During evolution SRCs have emerged from strong selection pressures and are thus regarded as key factors for human adaptation (7). The involvement of SRC family members in reproduction, energy metabolism, and growth outlines the importance of this class of molecules in human physiology and disease. As metabolism and growth are essential for survival and multiplication, cancer cells often hijack and co-opt these multifaceted “master” molecules to enhance their proliferative behavior. Thus, understanding the role of SRCs in energy homeostasis of cancer cells should shed light on additional roles for coactivators in cancer biology. Environmental stresses such as fluctuations in nutrient availability and dietary composition lead to various phenotypes in mouse models of coactivator gene disruption, indicating that SRCs can orchestrate broad transcriptional reprograms to utilize available nutrients for the maintenance of energy homeostasis. Ongoing and future studies will expand our understanding of NR coactivators in various human pathologies and should identify additional targeting strategies for therapeutic interventions in multiple diseases.

Glossary

NR	nuclear receptor
SRC	steroid receptor coactivator
HAT	histone acetyltransferase
CARM	coactivator-associated arginine methyltransferase
PTM	posttranslational modification
SUMO ligase	small ubiquitin-related modifier ligase
AR	androgen receptor
TNFα	tumor necrosis factor–alpha
MMP-9	matrix metalloproteinase–9

EMT

epithelial-mesenchymal transition

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SUMMARY POINTS

1. Transcriptional coactivators have emerged as the principal regulators of gene expression by directly interacting with and modulating the activity of essentially all nuclear receptors (NRs) and transcription factors.
2. SRCs were the first gene family to be classified and characterized as coactivators for NRs. Each member of the SRC family can enhance transcriptional activity of NRs by acting as a bridging molecule, assisting protein-protein interactions between NRs and multiple other coregulators, and facilitating the assembly of the transcriptome complex at target gene promoters.
3. Different combinatorial PTM codes on SRCs alter their conformation and affinity toward specific transcription-complex proteins to promote upstream-signal-specific genetic changes to execute physiological programs. Diverse sets of enzymes that interact with and modify SRCs include kinases, phosphatases, small ubiquitin-related modifier (SUMO) ligases, ubiquitin ligases, histone acetyltransferases, and histone methyltransferases.
4. NR coactivators have emerged as primary regulators of metabolic homeostasis, modulating energy balance in different tissues.
5. SRCs are often highly amplified and overexpressed in different types of malignancy, driving primary tumor growth, invasion-metastasis, and drug resistance.
6. Because they can integrate numerous upstream signaling events into functional outputs, coactivators are regarded as attractive therapeutic targets for the treatment of cancer.

Figure 1.

Nuclear receptor coactivators control the physiology of multiple organs that are critical for various metabolic disorders and some rare genetic diseases as well. Target genes transcriptionally regulated by the coactivators are indicated in red.

Figure 2.
Steroid receptor coactivators (SRC family members) are abundantly expressed and amplified in various forms of cancer.