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Editor

Encyclopedia of Signaling Molecules

With 686 Figures and 86 Tables

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STAT92E

▶ Phospho- and Unphospho-STATs in Signal Transduction and Gene Regulation (STAT)

STD

▶ ZAP-70

Sterile Alpha and TIR Motif-Containing Protein

▶ Toll-like Receptor Adaptor Protein Family Members

Sterile-Alpha Motif and Leucine Zipper–Containing Kinase AZK (ZAK)

▶ MLTK

Steroid Receptor Coactivator Family

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Synonyms

ACTR; AIB1; GRIP1; NcoA-1; NCoA-2; pCIP; RAC3; SRC-1; SRC-2; SRC-3; TIF2; TRAM-1

Historical Background

Steroid hormones have profound effects on physiology and behavior. Most of these biological effects of steroid hormones are mediated through their respective receptors, which are members of the steroid/nuclear receptor superfamily of transcriptional activators. These receptors can act in a classic genomic mechanism by interacting directly with DNA to alter transcription or at the membrane to rapidly activate cytoplasmic signaling pathways (Tetel and Lange 2009). In the classic genomic mechanism of action, nuclear receptor coregulators act to enhance (coactivators) or repress (corepressors) the transcriptional activity of these receptors. While over 300 coactivators have been identified to function in receptor transcription, the role of these coactivators in a wide range of human diseases is becoming better understood (Lonard et al. 2010). This review will focus on the function of the steroid receptor coactivator family as signaling molecules in physiology and behavior and in human disease.

p160 Steroid Receptor Coactivator Family

The steroid receptor coactivator (SRC) family of p160 proteins consists of SRC-1 (NcoA-1), SRC-2 (GRIP1/TIF2/NCoA-2), and SRC-3 (AIB1/TRAM-1/ACTR/RAC3/pCIP). The SRC family and the other nuclear receptor coactivators share a common set of characteristics. The SRC family of coactivators physically interacts with steroid receptors, including receptors for androgens (AR), estrogens (ER), progestins (PR), and glucocorticoids (GR), in a ligand-dependent manner (Johnson and O'Malley 2011). The SRCs physically associate with agonist-bound receptors through centrally located multiple LXXLL motifs (L, leucine; X, any amino acid) that make up nuclear receptor (NR) boxes. The SRCs, as well as other coactivators, do not bind DNA and thus differentiate them from traditional transcription factors. The C-terminus of the SRCs contains two activation domains (AD-1 and AD-2). The N-terminus contains a third activation domain (AD-3) and a bHLH-PAS motif (basic helix loop helix-Per Arnt Sims), which is the most conserved domain within this family of proteins. The activation domains interact with secondary coactivators known as co-coactivators. These co-coactivators act as bridging molecules between the receptor and the general transcription machinery and modify chromatin within the promoter and enhancer regions by histone acetylation and methylation (Johnson and O'Malley 2011).

p160 SRC Family in Physiology

SRC-1

In addition to what is known about the molecular mechanisms of the SRCs from in vitro studies, more is being learned about their role in hormone action in vivo. SRC-1 knockout mice, while fertile, have decreased responsiveness in progestin target tissues (Xu et al. 1998), partial resistance to thyroid hormone (Weiss et al. 1999), and delayed development of cerebellar Purkinje cells (Nishihara et al. 2003). Interestingly, in these mice SRC-2 is up-regulated in steroid-sensitive tissues, including brain and testes, suggesting that increased expression of SRC-2 compensates for the loss of SRC-1 (Xu et al. 1998).

SRC-2

Studies of SRC-2 knockout mice reveal that this coactivator is important in fertility and ductal branching in mammary gland (Fernandez-Valdivia et al. 2007). Disruption of SRC-2 expression in uterine PR-positive cells of $PR^{Cre/+}SRC\text{-}2^{flox/flox}$ mice led to an early block in embryo implantation (Fernandez-Valdivia et al. 2007). Furthermore, removal of SRC-1 in $PR^{Cre/+}SRC\text{-}2^{flox/flox}$ uteri caused a block in decidualization, suggesting that both SRC-1 and SRC-2 are required for complete PR-dependent decidualization. In addition, SRC-2 is important for PR action in mammary gland as demonstrated by the lack of significant branching and alveolar morphogenesis in the $PR^{Cre/+}SRC\text{-}2^{flox/flox}$ mammary gland (Fernandez-Valdivia et al. 2007). Microarray analysis of uteri from SRC-2 null mice reveals that SRC-2 is involved in the ability of progesterone to repress specific genes involved in a variety of functions, including cell cycle and immunity (Jeong et al. 2007).

SRC-3

Female SRC-3 null mice, while fertile, have delayed puberty and longer estrous cycles, ovulate fewer eggs, and have impaired mammary gland development (Han et al. 2006). Studies in SRC-3 null mice reveal that this coactivator is critical for normal PR-dependent mammary gland development and function (Han et al. 2006). Interestingly, gonadotropin-releasing hormone (GnRH) can activate PR-dependent transcription of a reporter gene in a pituitary cell line (An et al. 2006). Knockdown of SRC-3 by siRNA abolishes this effect, suggesting that SRC-3 is required for this GnRH-induced activation of PR (An et al. 2006).

p160 SRC Family in Metabolism and Adipogenesis

SRC-1

All three members of the p160 family of coactivators are involved in metabolic homeostasis and adipogenesis, which increases risk for clinical conditions including cardiovascular disease and diabetes. SRC-1 is critical in maintaining energy balance by regulating both energy intake and expenditure (Louet and O'Malley 2007). In support, SRC-1 knockout mice have decreased energy expenditure and a reduced thermogenic capacity and are, thus, prone to obesity. One proposed mechanism for SRC-1 in metabolism is through its interactions with PPARγ coactivator-1α (PGC-1α), a protein important in the control of mitochondrial biogenesis and oxidative phosphorylation (Louet and O'Malley 2007).

SRC-2

In contrast to SRC-1, SRC-2 knockout mice are leaner compared with wild type mice and have an increase in adaptive thermogenesis (Chopra et al. 2008). It appears that the absence of SRC-2 increases the interaction of SRC-1 with PGC-1α, enhancing thermogenic activity. Thus, it has been proposed that the ratio of SRC-1 and SRC-2 plays a role in maintaining the balance of energy expenditure and adipogenesis through controlling the metabolic activity of PGC-1α. In the liver, SRC-2 acts as a coactivator for the nuclear receptor RORα in the regulation of hepatic G6Pase, an important regulator of glucose production. Ablation of SRC-2 in mice leads to phenotypes of Von Gierke's disease, an inherited glycogen storage disease (Chopra et al. 2008).

SRC-3

SRC-3 knockout mice have lower body fat content compared with wild type animals (Louet and O'Malley 2007). SRC-3 controls the transcription of PPARγ2, important for adipocyte differentiation through enhancing the CAAT enhancer binding protein-β (Chopra et al. 2008). In support, adipocyte

differentiation and adipogenesis were impaired in both mouse embryonic fibroblasts from cells isolated from SRC-3 knockout mice and a knockdown of SRC-3 in 3T3-L1 adipocyte cells (Chopra et al. 2008). However, a knockdown of SRC-1 and SRC-2 had little effect on adipocyte differentiation. Taken together, these studies suggest that all three members of the p160 family of coactivators play an important role in energy homeostasis and adipogenesis.

SRC Family Functions in Brain and Behavior

A variety of recent studies indicate that two of the p160 SRC family members, SRC-1 and SRC-2, are important for hormone action in brain and the regulation of behavior (Tetel et al. 2009).

SRC-1 is expressed at high levels in the hypothalamus, cortex, and hippocampus of rodents (Tetel et al. 2009). Moreover, SRC-1 is expressed in the majority of estradiol-induced PR cells in regions involved in metabolism and female reproduction, including the ventromedial nucleus of the hypothalamus (VMN), medial preoptic area, and arcuate nucleus in rodents (Tognoni et al. 2011). Furthermore, SRC-1 interacts with steroid receptors; recent studies reveal that SRC-1 from brain physically associates with ER and PR in a receptor subtype- and brain region-specific manner (Molenda-Figueira et al. 2008). SRC-1 is critical for normal development of hormone-dependent sexual differentiation of the brain and adult sexual behavior (Auger et al. 2000). In the adult brain, SRC-1 functions in the VMN to modulate ER-mediated transactivation of the behaviorally relevant PR gene (Molenda et al. 2002). In addition, SRC-1 functions in distinct ER- and PR-dependent aspects of female sexual behavior (Molenda-Figueira et al. 2006). Interestingly, reduction of SRC-1 expression in brain by antisense altered PR function and reduced PR-dependent proceptivity (behavior by the female to solicit interaction by the male), but not PR-dependent receptivity (Molenda-Figueira et al. 2006). These findings suggest that reduction of SRC-1 by antisense disrupted the activity of PR signaling pathway(s) that influence(s) proceptivity, while alternate PR signaling pathways, that regulate PR-dependent receptivity, remained intact and functional.

SRC-2 is coexpressed with PR and ERα in rodent hypothalamus and physically associates with these receptors in a hormone-dependent manner (Yore et al. 2010; Tognoni et al. 2011). In further support of a role for SRC-2 in hormone action in brain, SRC-2 functions in estradiol-induction of hypothalamic PR and female sexual behavior in mice and rats (Apostolakis et al. 2002). Interestingly, in contrast to the other members of the SRC family, *SRC-3* is only sparsely expressed in the hypothalamus and does not appear to modulate the expression of reproductive behavior (Apostolakis et al. 2002).

p160 SRC Family in Breast and Prostate Cancer

SRC-1

SRC-1 has been found to be elevated in breast tumors and a strong predictor of breast cancer recurrence and hormone-independent tumors. In vitro studies demonstrate that SRC-1 promotes cancer metastasis through the estrogenic pathway. MCF-7 breast cancer cells over-expressed with SRC-1 have increased expression of estrogen-induced genes and enhanced estrogen-induced cell growth. However, MCF-7 cells treated with antisense against SRC-1 show a decrease in cell proliferation and invasion, as well as a lower level of SDF-1α, a protein that controls cell proliferation through autocrine and paracrine mechanisms (Xu et al. 2009). These findings suggest that SRC-1 increases breast cancer cell proliferation through regulating the SDF-1α pathway.

SRC-1 promotes estrogen-independent breast cancer metastasis through the integrin α5 (ITGA5) signaling pathway. In ER-negative tumors, SRC-1 expression is positively correlated with ITGA5, an important molecule involved in mediating cell adhesion and migration (Qin et al. 2011). In further support of SRC-1 promoting cancer proliferation through an estrogen-independent pathway, ITGA5 promoter activity is enhanced by SRC-1.

In prostate cancer, SRC-1 is correlated with increased tumor aggressiveness and promotes cell proliferation by enhancing AR activation and function (Agoulnik et al. 2006). The phosphorylation of SRC-1 by mitogen-activated protein kinase (MAPK) leads to an increase in AR activity (Suzuki et al. 2003). Reduction of SRC-1 in AR-positive cell lines, but not in AR-negative cell lines, resulted in

decreased tumor proliferation, suggesting the major effect of SRC-1 is through the androgenic pathway.

SRC-2

The role of SRC-2 in oncogenesis remains controversial. While one study reported a correlation of SRC-2 with cyclin D1 in ERα-positive breast tumors, another study found no changes in SRC-2 levels (Xu et al. 2009). However, the over-expression of SRC-2 in MCF-7 breast cancer cells led to a decrease in cell proliferation and invasion and a reduction in the expression of ERα target genes. In prostate cancer, SRC-2 expression correlates with recurrence of the disease. The down-regulation of SRC-2 by antisense reduced expression of AR-induced genes and decreased cell proliferation in both AR-dependent and AR-independent prostate cancer cell lines (Agoulnik et al. 2006).

SRC-3

SRC-3 (aka amplified in breast cancer-1, AIB1) is highly over-expressed in breast cancer and is correlated with ER and PR expression and tumor size (Anzick et al. 1997; Bautista et al. 1998). SRC-3 expression is also correlated with poor clinical prognosis. Breast cancer cells transfected with SRC-3 had enhanced estrogen-dependent transcription, suggesting that SRC-3 promotes tumorigenesis through an estrogenic pathway (Lanz et al. 2010). Several mechanisms have been proposed on how SRC-3 acts to promote cancer growth. SRC-3 regulates E2F1-mediated cell cycle progression and GRB-2 associated binding protein2, which activates the AKT/► mTOR pathway and increases cancer growth. SRC-3 has also been shown to activate epidermal growth factor receptor EGFR and ERBB2, resulting in the hyperactivation of Akt and MAPK which contributes to cancer proliferation, growth, and migration (Yan et al. 2008). In further support, Akt signaling is down-regulated in SRC-3 knockout mice. In another study, SRC-3 increased PEA3 and AP-mediated matrix metalloproteinase expression which promote breast and prostate tumor cell metastasis (Yan et al. 2008).

In prostate cancer, SRC-3 is correlated with both tumor stage and poor clinical prognosis (Culig et al. 2004). SRC-3 is involved in the androgenic pathway by acting as a coactivator for AR. However, SRC-3 is also involved in androgen-independent cancer proliferation as the down-regulation of SRC-3 in androgen-insensitive prostate cancer cells also leads to a decrease in proliferation (Zou et al. 2006).

Summary

The p160 family of nuclear receptor coactivators has a critical role in modulating steroid receptor action and thus the appropriate cellular response to steroids. A variety of studies indicate that these coactivators are essential in physiology, including metabolism and adipogenesis. In addition, this family of coactivators functions in brain to regulate important aspects of steroid action and the regulation of behavior. Thus, it is no surprise that alteration of the function of these molecules can contribute to steroid-responsive cancers, such as breast and prostate cancer, in profound ways. The findings reviewed above indicate that each of these members of the p160 family of coactivators can mediate distinct signaling pathways of steroid receptors. Therefore, understanding the recruitment of different coactivator complexes to the promoter, which is likely to be cell- and tissue-specific, will be critical for understanding how hormones regulate complex physiological and behavioral events, as well as hormone-dependent diseases.

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STK17B

► DRAK2