Published in final edited form as:
Nat Rev Cancer. 2009 September ; 9(9): 615–630. doi:10.1038/nrc2695.

Normal and Cancer-Related Functions of the p160 Steroid Receptor Coactivator (SRC) Family

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Abstract

The three homologous members of the p160 SRC family (SRC-1, SRC-2 and SRC-3) mediate the transcriptional functions of nuclear receptors and other transcription factors, and are the most studied of all transcriptional coactivators. Recent work has indicated that the SRC genes are subject to amplification and overexpression in various human cancers. Some of the molecular mechanisms responsible for SRC overexpression along with the mechanisms by which SRCs promote breast and prostate cancer cell proliferation and survival have been identified, as have the specific contributions of individual SRC family members in spontaneous breast and prostate carcinogenesis in genetically manipulated mouse models. These studies have identified new challenges for cancer research and therapy.

Introduction

Nuclear hormone receptors (NRs) are ligand-dependent, DNA-binding transcription factors that regulate gene expression and various physiological functions. Understanding how NRs control gene transcription has been a long and difficult journey. Initially, it was thought that NRs enabled general transcription factors (GTFs) and RNA polymerase II to assemble at the promoter to turn on mRNA synthesis. However, work began in the 1970s to search for nuclear non histone helper proteins that were thought to aid the binding to DNA and the transcriptional function of NRs [1, 2]. The finding that activation of one overexpressed NR could indirectly inhibit the transcriptional activity of another NR[3, 4] and that *in vitro* transcription systems consisting of purified NRs and GTFs were inefficient further suggested that additional transcription activators were required for efficient hormone-induced transcriptional activation [5]. In 1995, the steroid receptor coactivator-1 (SRC-1) was cloned as the first authentic NR coactivator. SRC-1 interacted with steroid receptors in a hormone-dependent manner and robustly increased the transcriptional activities of steroid receptors [6]. Soon after, two other homologous proteins, SRC-2 (TIF2 or GRIP1) [7, 8] and SRC-3 (p/CIP, RAC3, AIB1, ACTR or TRAM-1) [9–13], were characterized as NR coactivators. These three homologous proteins comprise the p160 SRC family. In this review, we summarize our current knowledge regarding the molecular features, functional mechanisms, posttranslational modifications and physiological functions of the SRC family

Further Information

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members. Our major emphasis will be on the contributions and mechanisms of the SRC family in cancer.

Structural and functional characteristics of the SRC family

SRCs contain three structural domains. The N-terminal basic helix-loop-helix-Per/ARNT/Sim (bHLH-PAS) domain is the most conserved region and is required for protein-protein interactions [14–16]. The bHLH-PAS domain can interact with several transcription factors such as myogenin, MEF-2C and TEF to potentiate transcription [17, 18]. The central region contains three LXXLL (L for leucine and X for any amino acid) motifs, which form amphipathic α-helices and are responsible for interacting with NRs [19–21]. The C-terminus contains two transcriptional activation domains (AD1 and AD2). AD1 binds CBP and p300 histone acetyltransferase (HAT), and the recruitment of CBP or p300 by SRCs to the chromatin context is essential for SRC-mediated transcriptional activation. AD2 interacts with coactivator-associated arginine methyltransferase 1 (CARM1) and protein arginine methyltransferases (PRMT1), which are histone methyltransferases [22–29]. The C-termini of SRC-1 and SRC-3 contain HAT activity domains, although their cellular substrates are incompletely identified [12, 30]. These molecular features provide SRCs with a suitable structural base for recruiting additional coregulators and general transcription factors, which in turn results in chromatin remodeling, assembly of general transcription factors and recruitment of RNA Polymerase II for transcriptional activation [31, 32]. The basic SRC structural domains and the simplified functional mechanisms for SRCs in NR-dependent transcriptional activation are sketched in Fig. 1.

In addition to serving as coactivators for NRs, SRCs also serve as coactivators for other transcription factors, including NF-κB, Smads, E2F1, STATs, HIF1, p53 and RB (Table 1). SRCs also can promote gene transcription by interacting with kinases, phosphatases, ubiquitin/sumo ligases, histone acetyltransferases and histone methyltransferases (Table 1). By modulating gene expression controlled by a broad range of NRs and non-NR transcription factors, SRCs regulate many diverse physiological functions.

The molecular targets of SRCs are numerous (Box 1). Genetic ablation of SRC-1 altered gene expression patterns involved in cell cycle and energy metabolism pathways such as glycolysis, glycogen synthesis and fatty acid synthesis [33]. Genetic ablation of SRC-2 increased gene expression for energy expenditure but decreased gene expression for energy storage [33]. SRC-3 is required for the expression of several genes for cell cycle and apoptosis in breast cancer cells [34].

Box 1

SRC knockout mice

Although SRC-1 null (*Src1*$^{-/-}$) mice display no gross defects in development and growth, careful analyses revealed that SRC-1 plays important *in vivo* roles in organ physiology. In reproductive organs, SRC-1 deficiency reduces oestrogen-induced uterine growth, oestrogen- and progesterone-dependent uterine decidual response, mammary gland ductal side branching and alveolar formation, and testosterone-stimulated prostate growth [139]. In addition to partial resistance to sex steroids, partial resistance to thyroid hormone (RTH) also exists in *Src1*$^{-/-}$ mice[140,141]. In the liver, SRC-1 is an essential coactivator for CEBPα, which together with PPARγ regulates the pyruvate carboxylase gene, the limiting enzyme for gluconeogenesis. In brown fat, activation of PPARγ triggers the recruitment of a coactivator complex containing PGC-1, SRC-1 and CBP/p300 [142] and inactivation of SRC-1 impairs the thermogenic activity of PGC-1, decreasing energy expenditure and resulting in obesity with a high fat diet [143].

Assessment of *Src2*$^{-/-}$ (*Tif2*$^{-/-}$) mice demonstrated an important function of SRC-2 in reproductive organs and in the regulation of metabolism. *Src2*$^{-/-}$ Sertoli cells are unable to support normal spermatogenesis[144] and SRC-2 is the dominant member of the SRC family that mediates androgen receptor function in the testis [145]. The hypofertility of female *Src2*$^{-/-}$ mice is partially due to a placental hypoplasia [144] and specific ablation of SRC-2 in the PR-positive cell linage inhibits the progesterone-induced decidual response and causes a block in embryo implantation. SRC-2 ablation also results in reduced ductal side branching and alveologenesis in the mammary gland [137]. In white adipose tissue, SRC-2 deficiency increases leptin expression and decreases the expression of genes responsible for anti-lipolysis and fatty acid uptake and trapping. In brown adipose tissue, SRC-2 deficiency increases levels of UCP-1, PGC-1 and acetyl CoA oxidase, promoting energy expenditure. As a result, *Src2*$^{-/-}$ mice exhibit higher body temperature under cold conditions, less fat accumulation, lower levels of fasting glycemia and triglycerides, and higher insulin sensitivity [143]. In the liver, SRC-2 enhances RORα-mediated G6Pase expression to regulate fasting hepatic glucose release from the liver. SRC-2 ablation recapitulates the human syndrome of Von Gierke's disease (glycogen storage disease-1a) [146].

Src3$^{-/-}$ mice show growth retardation, delayed puberty, reduced female reproductive function and blunted mammary gland development [147, 148]. In agreement with the growth retardation, circulating IGF-I levels in *Src3*$^{-/-}$ mice are significantly reduced. SRC-3 is required for vitamin D receptor-mediated expression of IGFBP-3, a binding protein maintaining IGF-I stability in the circulation [149]. In the mammary gland, SRC-3 deficiency decreases oestrogen and progesterone-induced mammary ductal growth and alveologenesis, revealing SRC-3's role in ER and PR function [147]. SRC-3 is not required for castration-induced regression and testosterone-stimulated regeneration of the prostate in mice, suggesting that SRC-3 is not essential for androgen and androgen receptor-dependent prostate morphogenesis [118].

Four SRC-1 splicing isoforms have been reported [35]. In comparison with SRC-1a, SRC-1b lacks a N-terminal region, while SRC-1c, SRC-1d and SRC-1e differ from SRC-1a and from each other at their unique C-terminal sequences. It has been shown that SRC-1a and SRC-1b have different abilities to enhance ERα activity in cultured cells [36]. A SRC-3 isoform, AIB1-Δ3, also has been reported [37]. AIB1-Δ3 lacks the N-terminal PAS/bHLH domain and it may be a more active coactivator for ERα and PR compared with the full-length SRC-3. However, the *in vivo* expression profiles and physiological significances of these SRC-1 and SRC-3 isoforms are currently unclear.

Posttranslational modifications of SRCs

The limiting concentrations of cellular SRCs suggest that changes in SRC levels and/or activities are efficient means for the cell to regulate gene expression. A number of studies have demonstrated that signaling pathways activated by extracellular stimuli such as hormones, growth factors and cytokines induce multiple posttranslational modifications of SRCs, including phosphorylation, ubiquitination, sumoylation, acetylation and methylation (Fig. 2). These dynamic and often reversible post translational modifications have crucial roles in determining the protein stability, the transcription factor-interactive specificity and the transcriptional activity of SRCs, and they link SRC functions to cellular responses to environmental cues. Deregulated post translational modifcation of SRC molecules have significant implications in human diseases such as cancer.

Phosphorylation

Phosphorylation of SRCs changes their affinity for select NRs and modulates NR-dependent gene expression [38–41]. Epidermal growth factor (EGF), interleukin 6 (IL-6) and cAMP treatments stimulate proline-directed kinase phosphorylation of SRC-1 on Thr1179 and Ser1185 and phosphorylated SRC-1 has higher coactivator function in both ligand-dependent and ligand-independent NR pathways [39, 42]. Interestingly, EGF induced phosphorylation of SRC-1 enhances progesterone receptor (PR)-dependent transcription [39]; IL6 mediated SRC-1 phosphorylation promotes androgen receptor (AR)-dependent transcription in a ligand-independent manner [42]; and cAMP induced phosphorylation of SRC-1 enables recruitment of p300 and CBP and PR-dependent transcription in a ligand-independent manner [43]. Furthermore, MAPK-mediated phosphorylation of SRC-1 on Thr1179 and Ser1185 increase its affinity for AR in prostate cancer cells, perhaps contributing to prostate cancer recurrence [42, 44]. In endometrial cancer cells, Src-mediated SRC-1 phosphorylation significantly increases the agonist activity of tamoxifen, indicating that SRC-1 has a role in tamoxifen-induced endometrial proliferation and increase the risk of endometrial cancer associated with use of tamoxifen [45, 46].

For SRC-2, Ser736 is phosphorylated by MAPKs, including oestrogen-induced p38 and EGF-induced ERKs. Phosphorylation of Ser736 enhances SRC-2 and p300/CBP interaction and increases SRC-2 coactivation function for oestrogen receptor α (ERα), PR and AR [38, 44, 47]. Protein kinase A (PKA) also phosphorylates SRC-2, resulting in a rapid increase in SRC-2 coactivator activity followed by accelerated SRC-2 degradation [48, 49].

In SRC-3, seven Ser/Thr (Thr24, Ser505, Ser543, Ser601, Ser857, Ser860 and Ser867) and one Tyr (Tyr1357) phosphorylation sites are functionally important [40, 41, 50]. The kinases that phosphorylate and activate SRC-3 include MAPK, IKK, Akt (by inhibiting GSK3) and CK1δ, suggesting a role for SRC-3 in accepting signals from multiple pathways. SRC-3 is also a target of the c-Abl tyrosine kinase that can be activated by oestrogen and growth factors. Phosphorylation of Tyr1357 by c-Abl facilitates SRC-3 action in mediating ERα, PR and NF-κB-dependent transcription by enhancing SRC-3 binding to p300 and transcription factors [50]. Importantly, Tyr1357 phosphorylation is elevated in ERBB2-induced mouse breast tumors, suggesting that phosphor-Tyr1357 plays a role in oncogenesis. Moreover, levels of SRC-3 Tyr1357 phosphorylation might serve as a marker for evaluating the efficacy of tyrosine kinase inhibitors.

Clinical studies have shown that SRC-3 expression levels are increased in a subset of breast tumors, and high SRC-3 levels are commonly associated with ERBB2 expression, tamoxifen resistance, disease recurrence and poor prognosis [51–53]. This unfavorable outcome can be explained by a series of linked molecular events. ERBB2 expression activates MAPK and Akt and causes phosphorylation of SRC-3 and ER, resulting in transcriptional activation and cell proliferation. Furthermore, Akt can stabilize SRC-3 by inhibiting GSK3 [54], suggesting a positive feedback mechanism between SRC-3 levels and Akt activity. Akt over activation is frequently observed in human cancers.

Interestingly, SRC-3 function and cellular concentrations are counter-regulated by kinases and phosphatases. Phosphatases PDXP and PP2A dephosphorylate SRC-3, inhibit SRC-3 interaction with ER and reduce SRC-3 coactivator activity [55]. Phosphatase PP1 de-phosphorylates phospho-Serines 101 and 102, which decreases SRC-3 transcriptional activity and increases SRC-3 stability [55] (Fig. 2). In contrast, atypical PKC (aPKC)-mediated SRC-3 phosphorylation stabilizes SRC-3 by targeting an acidic region of amino acid residues 1031–1097 and preventing SRC-3 from interacting with the C8 subunit of the 20S core proteasome [56]. Since both aPKC and SRC-3 are frequently overexpressed in cancers, they may synergistically promote carcinogenesis.

The transcriptional activities of SRCs also are regulated by subcellular localization and intracellular trafficking. SRCs contain nuclear import and export signals and locate in both cytoplasm and nucleus [57–59]. Post translational modifications can alter the availability of SRCs in a subcellular compartment by regulating their nucleo-cytoplasmic trafficking. For example, TNFα and EGF-induced phopshorylation of SRC-3 causes its redistribution from cytoplasm to nucleus [60, 61].In the cytoplasm, oestrogen-induced SRC-3 phosphorylation leads to SRC-3 and ERα interaction, suggesting that activation of SRC-3 may play a role in oestrogen-induced non-genomic effects [62]. SRC-3 also is associated with and phosphorylated by IKK and c-Abl in the cytoplasm in response to TNFα or growth factor stimulation, indicating a role for SRC-3 in these kinase pathways [50, 61]. Furthermore, SRC-3 can interact with TIA-1 and TIAR, two translational repressors associated with AU-rich regions in the 3'-UTR of cytokine mRNAs in the cytoplasm, thereby inhibiting translation of IL-1, IL-6 and TNF-α mRNAs [63].

Ubiquitination

26S proteasome-mediated degradation regulates the function of NRs and the turnover of activated NRs and SRCs [64–68]. Recently, two SCF-dependent mono-ubiquitination sites (Lys723 and Lys786) within the NR interaction domain of SRC-3 were identified [54]. Phosphorylation of Ser505 by GSK3 and Ser860 by p38 MAPK not only enhances SRC-3 interaction with ER and AR but also regulates its ubiquitination and protein stability [54, 69]. Sequential phosphorylation-dependent mono- to poly-ubiquitination events couple transcriptional activation with SRC-3 degradation, ensuring a proper termination of transcription (Fig. 2). In contrast to GSK3-mediated phosphorylation that causes SRC-3 degradation, aPKC-mediated SRC-3 phosphorylation protects SRC-3 from proteasomal degradation in an ERα-dependent manner, leading to an increased oestrogen-induced breast cancer cell growth [56].

Although the structure of the small ubiqitin-related modifier (SUMO) is similar to ubiquitin, the fate of a sumoylated protein is usually distinct from that of a ubiquitinated protein. Sumoylation can either antagonize SRC ubiquitination by targeting a common lysine substrate to prevent degradation and enhance its concentration, or change SRC into an inactive confirmation [70–76] (Fig. 2). In addition to ubiquitin-dependent turnover, REGγ, a proteasome activator that stimulates the trypsin-like activity of the 20S proteasome, binds and promotes SRC-3 degradation in a ubiquitin- and ATP-independent manner [77].

Acetylation and methylation

The function of SRCs can be modulated by acetylation. After transcriptional initiation, SRC-3 is acetylated by p300/CBP, resulting in disassembly of the NR and SRC-3 complex and termination of transcription [78] (Fig. 2). After initial stimulation, oestrogen treatment enhances CARM-1-mediated SRC-3 methylation on Arg1171 and terminates transcription by disassembling the SRC-3 coactivator complexes [79] and increasing SRC-3 degradation [80] (Fig. 2).

Combined posttranslational modifications

Different combinations of posttranslational modifications determine SRC coactivator potency and selectivity and allow SRCs to integrate multiple upstream signals into finely tuned regulation of gene expression. For example, retinoic acid and p38 MAPK-induced SRC-3 phosphorylation initially enhances SRC-3 interaction with retinoic acid receptor α (RARα) to activate transcription. Subsequently, the phosphorylated SRC-3 is subjected to ubiquitination and degradation, thereby leading to transcriptional termination. Another study demonstrated that phosphorylation of SRC-3 on Ser509 primed it for phosphorylation on Ser505. This then triggered SRC-3 mono- and subsequent poly-ubiquitination, which are

responsible for activation and degradation of SRC-3, respectively [54] (Fig. 2). Oestrogen-induced MAPK-dependent SRC-3 phosphorylation inhibited SRC-3 sumoylation conversely, de-phosphorylation increased SRC-3 sumoylation and decreased SRC-3 activity [76]. As ubiquitination and sumoylation can occur on the same lysine residue, different phosphorylation codes may determine whether SRC-3 is ubiquitinated or sumoylated, methylated or acetylated. As postranslational modifications largely influence both the cellular concentrations and the coactivator activities of SRCs, interventions that modulate SRC post translational modification have potential for controlling the detrimental roles of overexpressed SRCs in cancer.

In vivo functions of SRC Family Members

Our knowledge of the diverse *in vivo* functions of the SRC family is primarily gleaned from the characterization of knockout mouse models (Box 1). These studies indicate that each SRC family member has specific physiological functions. However, the additive severity of the phenotypes observed in double knockout mice indicates certain cooperative physiological functions among SRC family members. Most $Src1^{-/-};Src2^{-/-}$ mice do not survive and male and female $Src1^{+/-};Src2^{-/-}$ mice are completely infertile[81]. SRC-1 and SRC-3 cooperatively regulate viability, metabolism and energy balance. Most $Src1^{-/-};Src3^{-/-}$ mice die before birth, and mice that do survive exhibit compromised regulation of selective PPARγ target genes involved in adipogenesis and mitochondrial uncoupling, a higher leptin level, a developmental arrest in interscapular brown fat and a defect in adaptive thermogenesis. As a result, these mice eat more, but are lean and resistant to high-fat-diet-induced obesity due to a high basal metabolic rate and increased physical activity [82].

SRC genes in cancer

Each SRC has been found to be overexpressed in many types of human cancer, and in steroid hormone-promoted breast and prostate cancers in particular. Amplification of *SRC1* or *SRC2* is rare in cancers — by contrast, *SRC3* on human chromosome 20q21 is more frequently amplified in cancer (Table 2, a–c). The precise mechanisms that underlie over expression of SRCs in human cancer are still unclear. Many studies have investigated the mechanisms through which SRCs promote carcinogenesis and indicate that SRCs have important and distinct roles in promoting cancer initiation, progression and metastasis through alterations of multiple signaling pathways (Fig. 3).

SRC expression and function in breast cancer

In normal human breast, the levels of the three SRC proteins in epithelial cells are variable, but they are usually low or undetectable as assayed by immunohistochemistry (IHC) [83–88]. A number of studies examined the expression profiles of SRC mRNA and protein levels in human breast tumors and these data are considered below alongside data from mouse models and cell lines.

SRC1

Several studies demonstrated that SRC-1 protein is significantly elevated in 19% to 29% of breast tumors [83–86]. More importantly, SRC-1 elevation positively correlates with ERBB2 expression, lymph node metastasis, disease recurrence and poor disease-free survival (DFS) (Table 2a) [83–85]. Interestingly, a recent clinical study revealed elevated SRC-1 to be an excellent independent predictor of breast cancer recurrence following therapy [89].

In vitro, SRC-1 plays a role in cancer cell proliferation and invasion through multiple pathways. In MCF-7 breast cancer cells, SRC-1 overexpression potentiates cell growth stimulated by oestrogen in accordance with an increase in expression of oestrogen-responsive genes, indicating that SRC-1 plays an important role in oestrogen receptor-mediated cell growth[90]. In contrast, reduction of SRC-1 in MCF-7 cells decreases oestrogen-dependent DNA synthesis and the oestrogen-responsive pS2 gene expression [91]. Interestingly, MUC1, an ERα interactive protein overexpressed in breast carcinomas, can stimulate ERα-mediated transcription by aiding SRC-1 recruitment to oestrogen-responsive promoters, suggesting that SRC-1 acts in MUC1-stimulated cell growth [92]. Furthermore, MCF-7 cells lacking SRC-1 do not show increases in oestrogen-induced SDF-1α expression and cell proliferation and invasion, suggesting that SRC-1 may regulate cell proliferation and invasion through autocrine/paracrine activity of the SDF-1α–CXCL12 signaling pathway [93].

In MMTV-polyoma middle T (PyMT) mammary tumor-prone mice, SRC-1 levels are increased during tumorigenesis. Knockout of *Src1* does not affect PyMT-induced mammary tumor initiation and growth, but it helps to maintain epithelial differentiation and polarity, and importantly, prevents tumor cell metastasis to the lung. Further analyses revealed that SRC-1 deficiency reduced ERBB2 expression and Akt activation and also inhibited colony stimulating factor 1 (CSF-1) expression and macrophage recruitment to the tumor site [94]. In addition, a recent study demonstrated that SRC-1 promotes epithelial-mesenchymal transition (EMT), migration, invasion and metastasis of mammary tumor cells by coactivating PEA3-mediated Twist expression [95].

SRC2

One study reported no significant change in the levels of SRC-2 protein in breast tumors, while another study reported the correlation of SRC-2 with cyclin D1 expression in ERα+ breast tumors [86, 96] (Table 2b). In MCF-7 breast cancer cells, knockdown of SRC-2 reduces oestrogen-induced cell proliferation and target gene expression [91] and like SRC-1, SRC-2 overexpression may also promote cell proliferation and invasion through inducing SDF-1α expression [93].

SRC3

In separate studies of breast tumors, the frequencies of *SRC3* amplification were 9.5% as measured by FISH [11] and 4.8% as measured by Southern blot [97]. The levels of SRC-3 mRNA and protein in breast cancer have been extensively analyzed. SRC-3 mRNA overexpression was found in 64% [11], 31.6% [98], 31% [51] and 13% [99] of independent breast tumor cohorts. SRC-3 protein overproduction was identified in 9.8% [87] and 20% [86] of two different breast tumor cohorts. Interestingly, SRC-3 overexpression in breast cancer usually correlates with the expression of ERBB2, matrix metalloproteinase 2 (MMP2), MMP9 and PEA3 and with larger tumor size, higher tumor grade, and/or poor DFS [11, 51, 52, 86, 88, 96–98] (Table 2c). In tamoxifen-treated patients, high levels of SRC-3 expression are associated with tamoxifen resistance and a poorer DFS. Importantly, patients with high levels of both SRC-3 and ERBB2 exhibit early and severe resistance to selective oestrogen receptor modulators (SERM) therapy [52]. As ERBB2 activates MAPK, which in turn phosphorylates ER and activates SRC-3 [100], the overexpression of both ERBB2 and SRC-3 significantly enhances the agonist activity of tamoxifen and therefore, reduces its antitumor activity in patients with breast cancer [101].

In breast cancer cells, SRC-3 can be recruited to the oestrogen responsive *CCND1* promoter to enhance cyclin D1 expression [102] – depletion of SRC-3 in MCF-7 cells significantly reduces oestrogen-mediated cell proliferation and survival. Down-regulation of SRC-3 in

MCF-7 cells also reduces oestrogen-dependent colony formation in soft agar and tumor growth in nude mice [103].

The *in vivo* role of SRC-3 in breast cancer initiation and progression has been investigated in multiple mouse models. In mice harboring the MMTV–v-*ras* (*ras*) transgene, breast tumor incidence was reduced dramatically in *Src3*$^{-/-}$;*ras* virgin mice and inhibited completely in ovariectomized *Src3*$^{-/-}$;*ras* mice [104]. Breast tumor latency and growth were delayed significantly in *Src3*$^{-/-}$;*ras* virgin mice with natural oestrous cycles, multiparous mice with cyclically elevated reproductive hormones and virgin mice bearing pituitary isografts with persistently elevated hormones. Interestingly, SRC-3 deficiency did not alter the expression of oestrogen and progesterone-responsive genes in the mammary gland and tumors, but it caused partial resistance to insulin-like growth factor I (IGF1) because of a significant reduction in insulin receptor substrate-1 (IRS-1) and IRS-2. The impaired IGF-I signaling pathway in *Src3*$^{-/-}$;*ras* mammary epithelium and tumor cells may be responsible in part for the suppression of mammary tumorigenesis and metastasis.

In a second model, the role of SRC-3 in susceptibility of the mammary gland to chemical carcinogens was characterized [105]. This study demonstrated that mammary ductal outgrowths emanating from the *Src3*$^{-/-}$ mammary epithelial transplants in WT mice were attenuated, indicating that the role of SRC-3 in mammary ductal growth is mammary epithelial cell autonomous. In mice treated with the chemical carcinogen 7,12-dimethylbenz[a]anthracene (DMBA), SRC-3 deficiency protected the mammary gland, but not the skin, from tumorigenesis. In this model, SRC-3 deficiency also suppressed the up-regulation of both IRS-1 and IRS-2 and thereby inhibited the activation of Akt, the expression of cyclin D1 and cell proliferation.

In a third model, the role of SRC-3 in breast tumorigenesis was assessed in MMTV-*Erbb2*-induced mammary tumorigenesis in WT and *Src3*$^{-/-}$ mice [106]. This study showed that ERBB2-induced mammary tumor development was significantly delayed in *Src3*$^{+/-}$ mice and completely suppressed in *Src3*$^{-/-}$ mice. In comparison with WT;*Erbb2* tumors, *Src3*$^{+/-}$;*Erbb2* tumors exhibited a decrease in phosphorylated ERBB2, cyclin D1 and cyclin E, reduced activity of Akt and JNK, and decreased cell proliferation. These findings suggest that SRC-3 is required for ERBB2 oncogenic activity and SRC-3 reduction in the mammary epithelium should potentiate therapies aimed at inhibiting ERBB2 signaling in breast cancer [106].

In a fourth model, the role of SRC-3 in breast cancer metastasis was investigated by using MMTV-PyMT mice [88]. This study demonstrated that genetic ablation of *Src3* in MMTV-PyMT mice significantly reduced lung metastasis and the effect was cell autonomous. Cellular and molecular analyses revealed that SRC-3 interacted with PEA3 and directly enhanced the activity of the MMP2 and MMP9 promoters and increased the expression of MMP2 and MMP9 in WT;PyMT tumor cells. Therefore, SRC-3 can aid breast cancer metastasis through MMP2- and MMP9-mediated EMT and cell invasiveness. This correlates with data from human breast tumors where SRC-3 expression is associated with high PEA3, MMP2 and MMP9 expression levels [88].

Finally and importantly, the oncogenic role of SRC-3 overexpression in the mammary gland was directly demonstrated by generating and characterizing MMTV-*Src3* transgenic mice. This study demonstrated that SRC-3 overexpression caused mammary hypertrophy, hyperplasia, abnormal post-weaning involution, and the spontaneous development of malignant mammary tumors. Tumor incidence was increased in other organs, including the pituitary and uterus [107]. In agreement with the down-regulation of the IGF-I signaling

pathway in *Src3*$^{-/-}$;*ras* mammary tumors [104], SRC-3 overexpression-induced mammary tumors have a hyperactive IGF-I signaling pathway [107].

In summary, consensus results indicate that both SRC-1 and SRC-3 are overexpressed in a subpopulation of breast cancers without clear relevance to ER and PR expression. Overproduction of SRC-1 and SRC-3 are generally detrimental to patients. SRC-2 expression profiles in breast cancer are less conclusive due to lack of sufficient data. Data from mouse models and cell lines indicate that SRC-1 and SRC-3 have important functions in breast cancer, including tumour initiation and progression. Data from SRC-3 mouse models highlight the oncogenic nature of this protein when its expression is deregulated.

Prostate cancer

The expression profiles of SRC family members have been investigated in prostate tumors (Table 2, a–c). Amplification of *SRC-1* is rare in human tumors and one study reported that *SRC1* was amplified in only 2 out of 70 specimens that included prostate cancer cell lines, xenografts and primary tumors[108]. However, several studies have found that the expression levels of both SRC-1 mRNA and protein are positively correlated with prostate tumor grades [109–111]. In addition, one study found more nuclear localized SRC-1 protein in androgen-independent prostate tumors [108], while another study using quantitative RT-PCR failed to detect significant correlations between SRC-1 mRNA and prostate tumor progression [112]. Overall, SRC-1 is thought to be elevated in certain prostate tumors, but its overexpression frequency has not been accurately determined.

In prostate cancer cells, SRC-1 is able to enhance AR-mediated cell proliferation in culture. *Src1* knockdown inhibits proliferation of the androgen-dependent LNCaP cells in culture. More interestingly, SRC-1 knockdown inhibits the growth of C4-2 prostate cancer cells that depend on AR for growth in androgen-depleted medium [109]. However, reduction of SRC-1 has no effect on the growth of the AR-negative PC-3 and DU145 prostate cancer cells [109]. These results suggest that SRC-1 promotes prostate cancer growth through enhancing AR function in an androgen-dependent and -independent manner.

The *in vivo* role of SRC-1 in prostate cancer has been investigated in transgenic adenocarcinoma of mouse prostate (TRAMP) mice harboring the SV40 large and small T antigen transgene driven by a probasin promoter[113]. During prostate carcinogenesis, SRC-1 protein levels remained constant in prostate tumors of TRAMP mice. TRAMP;*Src1*$^{-/-}$ mice exhibited similar prostate tumor initiation, progression and metastasis when compared to that observed in WT mice. Interestingly, in both WT and *Src1*$^{-/-}$ TRAMP mice, prostate carcinogenesis induced SRC-3 overexpression. Thus, the role of SRC-1 in murine prostate carcinogenesis may be nonessential due to possible compensations from SRC-3 or overexpression of other coactivators.

SRC-2 expression in prostate tumors was found to be elevated but the frequency of SRC-2 overexpression has not been characterized well. It was reported that SRC-2 expression in a subgroup of prostate cancer was positively associated with high tumor cell proliferation, high tumor grade and/or disease recurrence [110, 114]. In AR-positive prostate cancer cells, high levels of androgen repress SRC-2 expression. Depletion of SRC-2 reduces AR target gene expression, and inhibits proliferation of AR-dependent and AR-independent prostate cancer cells, suggesting that SRC-2 also enhances prostate cancer cell growth through both AR-dependent and AR-independent pathways [114].

SRC-3 expression in prostate tumors has been examined in two studies. One study with a small number of samples found that SRC-3 protein was overproduced in 38% of tumor samples [115]. The other study with a large number of tumor samples found that SRC-3 levels

were positively correlated with increasing PSA levels indicating tumour recurrence, Akt activation and tumor cell proliferation [116]. In prostate cancer cells, SRC-3 activates the Akt–mTOR signaling pathway and stimulates cell growth by increasing cell size. SRC-3 knockdown decreases cancer cell proliferation and xenograft tumor growth in nude mice and increases apoptosis [116, 117]. The role of SRC-3 in spontaneous prostate cancer was investigated by comparing tumor initiation and progression in TRAMP and TRAMP;*Src3*$^{-/-}$ mice [118]. SRC-3 was nonessential for normal androgen–AR-dependent prostate growth and high levels of SRC-3 expression were found in stromal and basal cells, but not in luminal epithelial cells. Of note, high levels of SRC-3 expression were detected in prostate tumor cells during progression toward more malignant stages. In agreement with this finding, development of prostate epithelial hyperplasia and the initiation of well-differentiated tumors were not affected by loss of SRC3, but it efficiently arrested prostate tumor growth and progression at the well-differentiated stage and significantly extended the animal life [118]. These results indicate that *de novo* induction of SRC-3 expression in partially transformed epithelial cells is essential for progression of prostate tumorigenesis into poorly differentiated carcinoma. Inhibition of SRC-3 expression or function in the prostate epithelium may be a potential strategy to suppress prostate cancer progression. Taken together, these findings suggest that overexpressed SRC family members have detrimental roles in promotion of prostate cancer initiation and progression.

Other cancers

The expression profiles of SRC family members in other types of cancers are summarized in Table 2, a–c). Briefly, in colorectal cancer, high levels of SRC-3 protein were detected in 35% tumors and were positively associated with tumor grades [119]. In endometrial carcinoma, one study reported an increase in SRC-1 and SRC-2 mRNAs [120], while another study reported a decrease in SRC-1 protein [121]. SRC-3 mRNA and protein levels were found to be increased in endometrial carcinomas, and various overexpression frequencies were reported in different studies [99, 120, 122]. SRC-3 overexpression was detected in 46% of esophageal squamous cell carcinomas and 40% of gastric cancers, and SRC-3 expression levels were positively associated with higher cell proliferation, metastasis and poor prognosis [123, 124]. Up-regulated SRC-3 protein was found in 64% of high-grade ovarian cancer specimens and 65% of pancreatic cancer specimens; SRC-3 levels in these cancers were positively correlated with disease degrees[125, 126].

An abnormal chromosomal rearrangement of inv(8)(p11p13) has been identified in a subset of patients with acute myeloid leukemia (AML) [127, 128]. This rearrangement results in a fusion between the 5’ portion of *MOZ* mRNA and the 3’ portion of *SRC2* mRNA; the fusion encodes a transcriptional activator domain that binds nucleosomes through MOZ and recruits CBP through a SRC-2 domain [127–129]. MOZ–SRC-2-transduced myeloid progenitors can be continuously passaged in culture and induce acute myeloid leukemia *in vivo* [130]. These findings reinforce the concept that deregulation of a transcriptional coactivator can lead to malignant disease in humans.

Intriguingly, one study reported that SRC-3 could inhibit IκB kinase to stabilize IκB and suppress NF-κB activation in the lymphoid lineage [131]. Genetic ablation of SRC-3 resulted in the release of IκB kinase inhibition and constitutive NF-κB activation. Consequently, a subset of old *Src3*$^{-/-}$ mice developed lymphocyte proliferation and spontaneous β-cell lymphoma [131]. Another study demonstrated that SRC-3 deficiency in macrophages did not affect NF-κB-mediated gene transcription, but inhibited the production of proinflammatory cytokines such as IL-1, IL-6 and TNF-α at the translational level [63]. It is currently unknown if the increased inflammatory cytokines in *Src3*$^{-/-}$ mice are responsible in part for the development of β-cell lymphoma. Taken together, these findings suggest that SRC-3

regulates cell proliferation in a cellular and signaling context-dependent manner, ranging from proliferative and tumorigenenic effects in most endocrine target organ epithelial cells to paradoxical antiproliferative effects in lymphoid cells.

Overall, one can conclude that miss-expression of SRC family members occurs not only in steroid hormone-promoted breast and prostate cancers but also in steroid-independent cancers, suggesting SRC family members promote carcinogenesis through both steroid dependent and independent pathways.

Summary and perspectives

Since SRC-1 was identified as a NR coactivator in 1995 [6], the NR coregulator field has experienced an explosion in research aimed at understanding the mechanism of NR coactivator function, much of which has been applied to studies of hormone-related cancers. Emanating from these studies, many previously unknown proteins such as SRCs, MTA1 and PGC-1 have been found to be 'Master Genetic Regulators' [2]. In this review, we have summarized our present knowledge about the molecular features, post translational modifications (Fig. 2), interactive proteins (Table 1), molecular targets and physiological functions of SRCs. By interacting with and coactivating most NRs and certain other transcription factors, SRCs coordinate expression of many genes directed to accomplishing larger physiological goals. Importantly, overexpression of SRC-3 in mammary epithelial cells has been shown to be sufficient to induce spontaneous mammary tumors in mice, indicating that overexpression of SRC-3 is oncogenic [107]. Conversely, knockout of SRC-3 in mice suppresses oncogene- and carcinogen-induced breast cancer initiation, progression and metastasis [88, 104–106]. However, knockout of SRC-3 only inhibits prostate cancer progression and metastasis and does not affect the initiation of prostate tumorigenesis in TRAMP mice [118]. Interestingly, knockout of SRC-1 only suppresses mammary tumor metastasis without affecting primary tumor formation, and does not affect prostate cancer initiation and progression [94, 95], suggesting differing contributions from SRC-1 and SRC-3.

Many studies have investigated the mechanisms responsible for SRCs to promote carcinogenesis. These studies revealed that SRC-1 can enhance the expression of ERBB2, colony stimulating factor 1 (CSF-1) and TWIST expression to promote breast cancer metastasis [94, 95]. SRC-3 overexpression can enhance v-*ras*-mediated cell transformation and activate ERα, EGFR and cyclin D1 expression, as well as the Akt pathway, MMPs and FAK to promote tumor initiation, growth and metastasis [88, 102, 104–106, 117, 132, 133].

Although progress has been made in understanding the function of SRCs in various cancers and the molecular mechanisms by which SRCs influence carcinogenesis, important questions remain to be addressed. First, the molecular mechanisms responsible for SRC-1 and SRC-3 gene amplification and mRNA overexpression in cancers are still not fully understood. A limited number of studies suggested that SRC-3 elevation in cancers might be attributed to both transcriptional activation and posttranslational stabilization. On one hand, SRC-3 serves as a coactivator for E2F1, which drives cell proliferation [134, 135]. Both E2F1 and SRC-3 can be tethered to the proximal region of the SRC-3 gene promoter through interacting with SP1, which enhances SRC-3 mRNA transcription. In this manner, E2F1 and SRC-3 form a positive regulatory loop that can constitutively enhance SRC-3 overexpression in cancer cells (Fig. 3) [136]. On the other hand, regulation of SRC-3 protein stability by posttranslational modifications represents another important mechanism for increasing SRC-3 protein levels in cancer (reviewed in preceding sections). Further investigations on the molecular mechanisms responsible for the miss-expression of SRC-3 and other SRC family members may provide approaches to reprogram their expression levels for cancer therapy.

Second, although some genes important for carcinogenesis and metastasis have been identified as SRC-regulated genes, a complete catalog of the direct targets of SRCs in cancer cells is still unavailable. Characterization of all SRC target genes and a proteomic profile of the transcription factors that work with SRCs will provide important insights into the gene networks and pathways used by SRCs to promote carcinogenesis. Third, most *in vivo* experiments to date have been carried out in knockout mice where certain systemic effects, such as changes in IGF-1 activity, exist. It will be important to further assess and validate the roles of SRCs in carcinogenesis by greater use of conditional knockout mice [137, 138] with cell type-specific Src ablations. In addition, development of stage-specific inactivation (or overexpression) of SRCs in breast and prostate tumors in mice will allow us to determine if SRCs are stage-dependent therapeutic targets. Finally, the most challenging of all tasks will be to translate the knowledge obtained from basic research to clinical applications and to develop clinically deliverable reagents that can counteract the excessive SRC activities in SRC-promoted cancers.

Online 'at-a-glance' summary

- SRC-1 was the first cloned steroid receptor coactivator that interacts with steroid hormone receptors to promote transcriptional activation in a hormone-dependent manner.
- The p160 SRC family contains three homologous members, SRC-1, SRC-2 and SRC-3. These SRCs interact with nuclear receptors and certain other transcription factors and recruit chromatin-remodeling and other transcriptional enzymes to facilitate the assembly of general transcription factors for transcriptional activation.
- SRCs are targets of multiple signaling pathways for posttranslational modifications. These posttranslational modifications determine or modulate SRC protein stability, subcellular localization, functional specificity, coactivator activity and/or coactivator complex assembly or disassembly.
- The phenotypes of knockout mice for individual and combinatorial SRC family genes revealed that SRCs are involved in many physiological processes and each SRC has both specific and redundant physiological functions in development and organ function.
- SRC-1 expression is elevated in a subset of breast cancers and is positively correlated with ERBB2 positivity and poor disease-free survival rate. Knockdown of SRC-1 in breast cancer cells inhibits cell proliferation.
- Knockout of SRC-1 in MMTV-PyMT mice suppresses metastasis without affecting primary tumor formation. SRC-1 promotes breast cancer metastasis through upregulating ERBB2, CSF-1 and Twist expression.
- Both gene amplification and overexpression of *SRC-3* are present in a subset of breast cancers. SRC-3 overexpression usually correlates with the expression of ERBB2, MMP2, MMP9 and PEA3 and with larger tumor size, higher tumor grade, and/or poor disease-free survival.
- SRC-3 plays an important role to promote breast tumor cell proliferation, migration, invasion and metastasis through many mechanisms such as enhancing ERα and E2F1 functions, IGF-I signaling pathway, EGF receptor and ERBB2 activation, as well as the expression of MMPs.

- Knockout of SRC-3 in mice suppresses mammary tumor initiation, growth and metastasis, while overexpression of SRC-3 in mouse mammary epithelial cells is sufficient to induce spontaneous mammary tumorigenesis.
- SRC-3 expression is elevated during prostate tumorigenesis in mice. Knockout of SRC-3 efficiently arrests prostate tumor progression at a well-differentiated stage.

Acknowledgments

This work was funded by National Institutes of Health grants (R01DK058242, R01CA112403 and R01CA119689 to J.X.; P01DK059820, R01HD07857 and R01HD08818 to B.W.O.), NIDDK-NURSA, an American Cancer Society Research Scholar Award (ACS #RSG-05-082-01 to J.X.), and a Susan Komen for the Cure Award (BCTR0707225 to R.W.).

Glossary terms

pS2 gene	The human pS2 gene in estrogen receptor α (ERα)-positive breast cancer cells such as MCF-7 cells is a direct target gene of ERα. Upon estrogen treatment, pS2 mRNA expression can be significantly induced within 15 minutes
Pituitary isograft	A pituitary gland isolated from a syngenic donor mouse is implanted into the kidney capsule of the recipient mouse. Upon the stimulation of the implanted pituitary isograft, the recipient mouse shows significantly increased levels of prolactin, progesterone and estradiol

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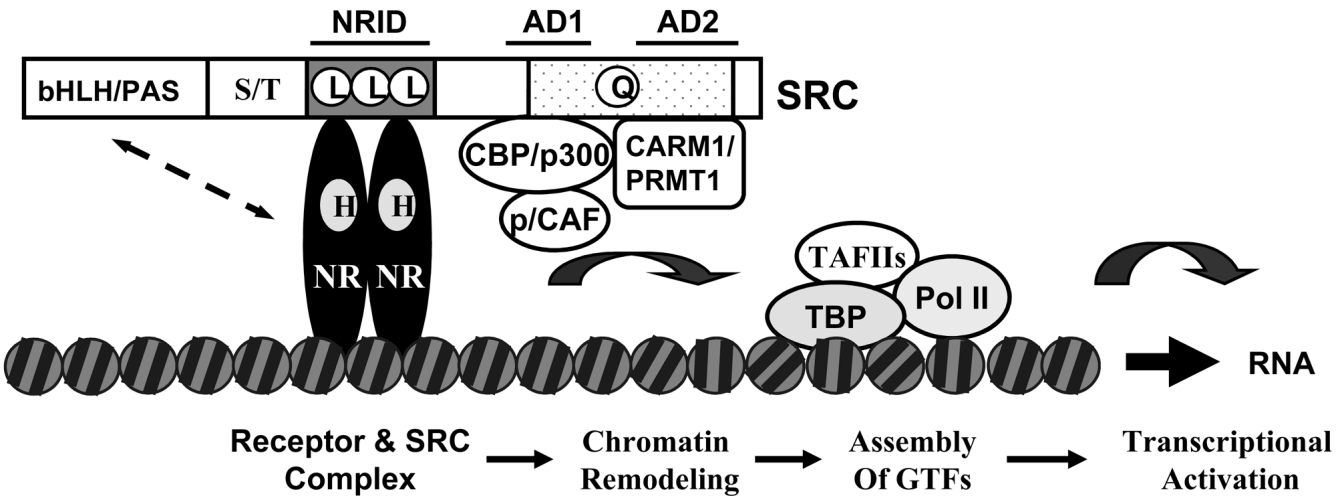

Fig. 1.

Molecular structure of SRCs and their functional mechanisms in steroid hormone-induced gene expression. The locations of basic structural and functional domains of SRCs are indicated. Upon hormone (H) binding, the hormone nuclear receptors (NR) expose their coactivator-binding motifs in their ligand-binding domains and allow SRCs to be recruited to the enhancer region of the NR target genes. SRCs further interact with CBP, p300, p/CAF, CARM1 and PRMT1 and recruit these common coactivators to the chromatin to build up a steroid receptor-directed transcriptional activation complex. This protein complex uses its protein acetyltransferase and methyltransferase activities to remodel the chromatin structure and to facilitate the assembly of general transcription factors and RNA polymerase II on the promoter for transcriptional activation. Of note, in addition to interactions between NR and the NRID domain of SRCs, interactions between NR and the bHLH/PAS domain of SRCs have been documented and may be important for function (see dotted line with arrowheads). Abbreviations: NRID, NR interaction domain; AD1 and AD2, activation domains 1 and 2; bHLH/PAS, the basis helix-loop-helix/Per-Ah receptor nuclear translocator-Sim domain; S/T, the serine and threonine-rich domain; L, L and L, the three LXXLL motifs responsible for interaction with nuclear receptors; Q, the glutamine-rich region; HAT, the histone acetyltransferase domain; CBP, the CREB (cAMP response element-binding protein) binding protein; p300, the 300 kDa protein homologous to CBP; p/CAF, the p300 and CBP-associated factor; CARM1, the coactivator-associated arginine methyltransferase 1; PRMT1, the protein arginine methyltransferase 1; TBP, the TATA binding protein; TAFIIs, TBP-associated general transcription factors (GTFs); Pol II, RNA polymerase II.

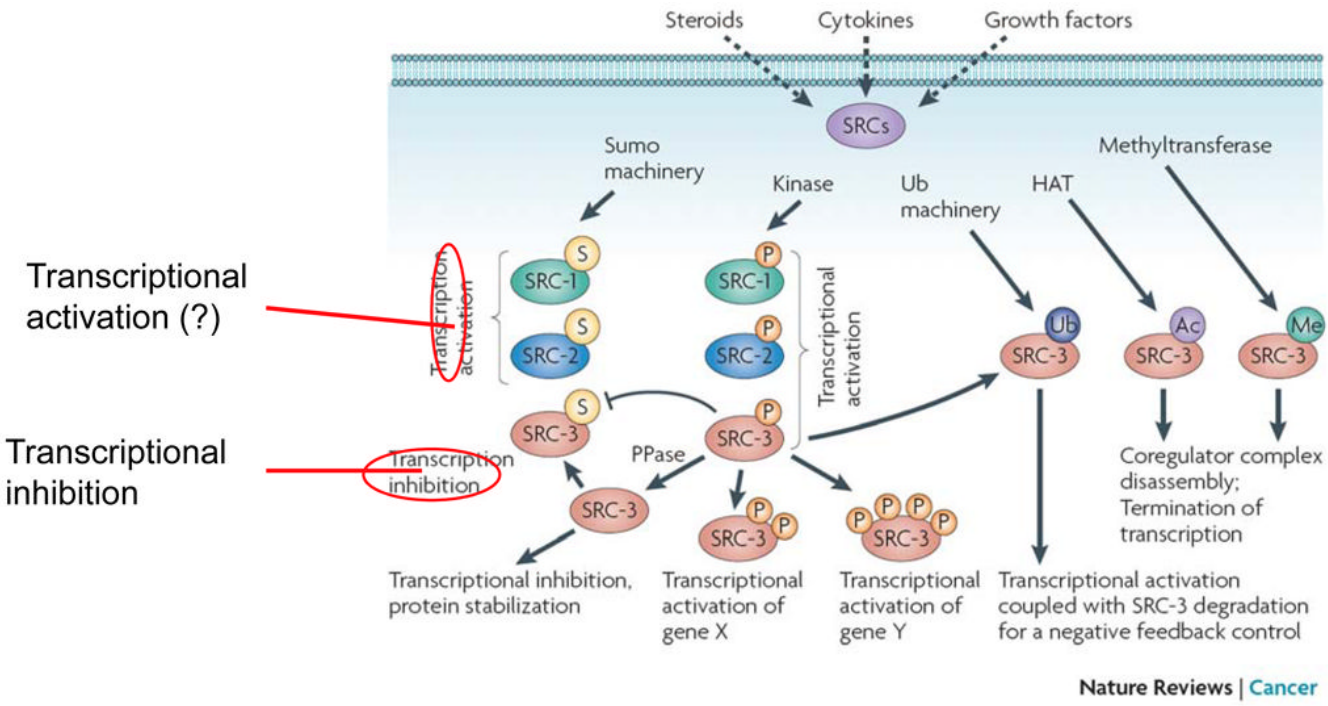

Fig. 2. Posttranslational modifications of SRCs

In general, phosphorylation results in activation of SRCs. In the case of SRC-3, phosphorylation determines the selectivity of SRC-3 for different transcription factors, promotes sequential ubiquitination of SRC-3 from mono-ubiquitination (activation) to poly-ubiquitination (degradation), and controls the duration of transcriptional activation by SRC-3. Conversely, de-phosphorylation by phosphatase (PPase) promotes SRC-3 sumoylation, stabilizes SRC-3 protein, and inhibits SRC-3 activity. Depending on specific kinases and phosphorylation sites, phosphorylation could either increase or decrease SRC-3 stability and cellular levels. Sumoylation enhances SRC-1 and SRC-2 activities (the "?" indicates that the conclusion is based on a limited amount of data), but it inhibits SRC-3 activity. SRC-3 acetylation and methylation cause a disassembly of the transcription complex and promote transcriptional termination.

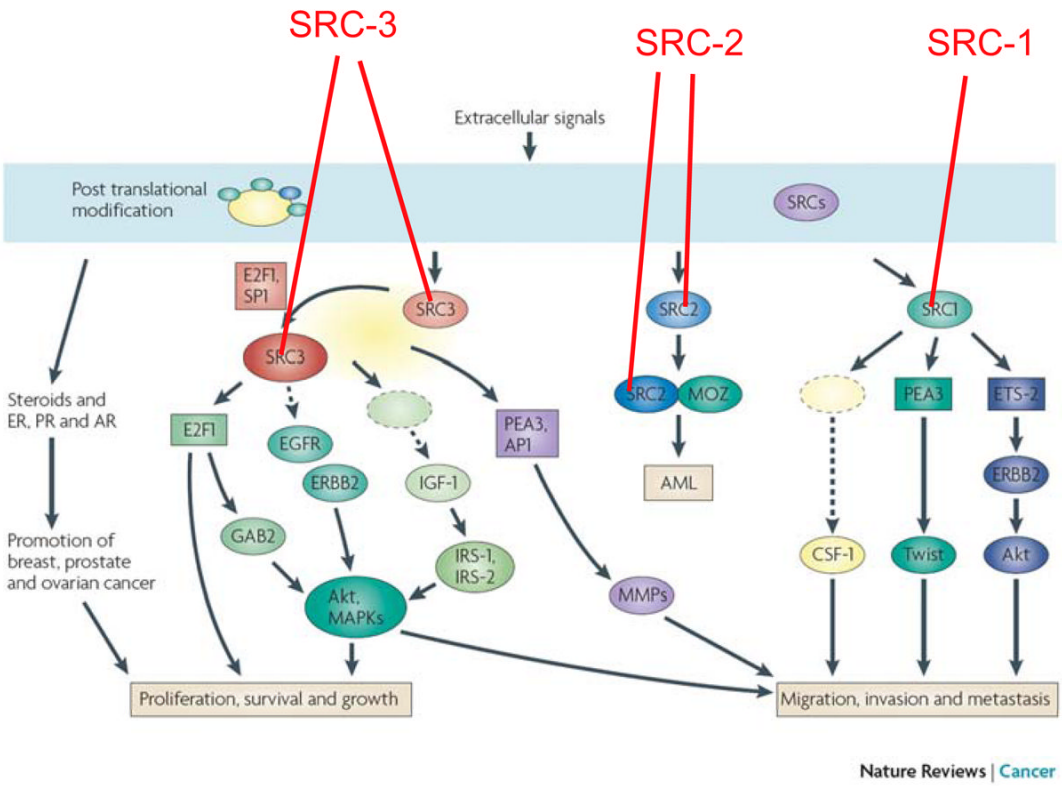

Fig. 3. SRCs promote carcinogenesis through multiple pathways

Extracellular signals and their signaling pathways cause posttranslational modifications of SRCs, which regulate the cellular concentrations, activities and specificities of SRCs. In general, SRCs enhance steroid receptor functions and facilitate hormonal promotion of breast, prostate and ovarian cancers. Specifically, SRC-1 enhances Ets-2-mediated HER2 expression and PEA3-mediated Twist expression and upregulates CSF-1 expression to promote breast tumor cell migration, invasion and metastasis. MOZ and SRC-2 fusion gene causes AML (acute myeloid leukemia). SRC-3 upregulates its own expression through serving as a coactivator for E2F1 and SP1. The overexpressed SRC-3 enhances PEA3 and AP-1 mediated MMP expression to promote breast and prostate tumor cell metastasis. SRC-3 also enhances E2F1-mediated cell cycle progression and Gab2 expression that activates Akt. In addition, SRC-3 upregulates IGF-I, IRS-1 and IRS-2 to promote the IGF-I signaling pathway and to activate EGFR and ERBB2 to enhance Akt and MAPK activities, resulting in hyperactivation of Akt and MAPK which contribute to cancer cell proliferation, growth, survival, migration, invasion and metastasis.

Table 1

List of proteins that interact with SRCs

Categories	Functional consequence	Method of detection	References
Transcription factors			
Nuclear receptors	activation	Co-IP, in vitro	150, 151
AhR/ARNT	activation	Co-IP, in vitro	152–154
AP-1	activation	Yeast 2-hybrid, in vitro	155
Brn-3	activation	Co-IP	156
β-catenin	activation	Mammalian 2-hybrid, in vitro	157
c-Ets	activation	Co-IP	158
E2F1	activation	Co-IP, in vitro	135
HNF4	activation	Yeast 2-hybrid	159, 160
IRF3	activation	Yeast 2-hybrid	161
MEF-2C	activation	Mammalian 2-hybrid, Co-IP, in vitro	18
NF-κB	activation	Co-IP	162
Smad3	activation	Co-IP, mammalian 1-hybrid	163
Tat	activation	Co-IP, in vitro	164
TEF-4	activation	Yeast 2-hybrid, in vitro	17
TTF1	activation	in vitro	165
Oncogene/Tumor suppressor			
HPV E7	suppression	Co-IP, in vitro	166
p53	activation	in vitro	167
Rb	activation	Co-IP, in vitro	168
Kinase/Phosphatase			
aPKC	phosphorylation, stabilization	Co-IP	56
c-Abl	phosphoryaltion, activation	Co-IP	50
GSK3	phosphorylation, activation, degradation	enzyme-substrate interaction	54
IKK	phosphorylation, activation	Co-IP	61
MAPK	phosphorylation, activation	enzyme-substrate interaction	42, 69
PDXP	dephosphorylation, suppression	enzyme-substrate interaction	55
PKA	phosphorylation, activation	enzyme-substrate interaction	43, 169
PP1	dephosphorylation, stabilization	enzyme-substrate interaction	55
PP2A	dephosphorylation, suppression	enzyme-substrate interaction	55
Ub/Sumo enzymes			
ARIP3/PIASxα	sumoylation, activation	in vitro	74
E6AP	ubiquitination, degradation	Co-IP, in vitro	170

Categories	Functional consequence	Method of detection	References
Fbw7	ubiquitination, activation, degradation	Co-IP	54
UBCH7	activation	Co-IP, in vitro	171
Coregulators			
ANCOS	suppression	Yeast 2-hybrid, Co-IP, in vitro	172
ASC	activation	Yeast 2-hybrid, in vitro	173
CARM1	activation, methylation, suppression	Yeast 2-hybrid, Co-IP	174
CoCoA	activation	Co-IP, in vitro	15
GAC63	activation	Co-IP, in vitro	14
GCN5	activation	Co-IP, yeast 2-hybrid	23
MMS19	activation	Yeast 2-hybrid, in vitro	175
p300/CBP	activation, acetylation, suppression	Co-IP, in vitro	35
PGC1	activation	in vitro	142
Others			
Cyclin T1	activation	in vitro	164
FLASH	activation, suppression	Yeast 2-hybrid, in vitro	176, 177
GAS	activation	in vitro	178
JAB1	activation	Yeast 2-hybrid, in vitro	179
Pin1	activation, degradation	in vitro	180
REGγ	degradation	Co-IP	77
SRA	activation	IP	181
TIA, TIAR	translational inhibition	Co-IP, in vitro	63

This is an incomplete list of SRC interactive proteins representing distinct categories. Co-IP, coimmunoprecipitation; IP, immunoprecipitation; in vitro, in vitro protein-protein interaction assay; AhR/ARNT, aryl hydrocarbon receptor/aryl hydrocarbon receptor nuclear translocator; AP-1, activator protein 1; Brn-3, POU domain, class 4, transcription factor 1; c-Ets, mammalian protooncogene homologue of the avian v-ets; E2F1, E2F transcription factor 1; HNF4, hepatic nuclear factor 4; IRF3, interferon regulatory factor 3; MEF-2C, myelin basic protein expression factor 2; NF-κB, nuclear factor of kappa light polypeptide gene enhancer in B-cells 1; Smad3, MAD homolog 3; Tat, Human immunodeficiency virus transactivator protein; TEF-4, transcriptional enhancer factor family of transcription factors; TTF1, thyroid transcription factor 1; p53, transformation related protein 53; Rb, retinoblastoma 1; APKC, atypical protein kinase C; c-Abl, c-abl oncogene 1, receptor tyrosine kinase; GSK3, glycogen synthase kinase 3; IKK, inhibitor of kappaB kinase; MAPK, mitogen-activated protein kinase; PDXP, pyridoxal (pyridoxine, vitamin B6) phosphatase; PKA, protein kinase A; PP1, protein phosphatase 1; PP2A, protein phosphatase 2; ARIP3/PIASxα, protein inhibitor of activated STAT 2; E6AP, ubiquitin protein ligase E3A; Fbw7, F-box and WD-40 domain protein 7; UBCH7, ubiquitin-conjugating enzyme E2L 3; ANCOS, ankyrin repeats containing cofactors; ASC, Activating signal cointegrator 1; CARM1, coactivator-associated arginine methyltransferase 1; CoCoA, calcium binding and coiled coil domain 1; GAC63, solute carrier family 30 (zinc transporter), member 9; GCN5, lysine acetyltransferase 2A; MMS19, MET18 S. cerevisiae; p300/CBP, E1A binding protein p300/CREB binding protein; PGC1, peroxisome proliferative activated receptor, gamma, coactivator 1; FLASH, caspase 8 associated protein 2; GAS, glutamate-rich coactivator interacting with SRC1; JAB1, JUN activation binding protein 1; Pin1, protein (peptidyl-prolyl cis/trans isomerase) NIMA-interacting 1; REGγ, proteaseome (prosome, macropain) 28 subunit, 3; SRA, steroid receptor RNA activator; TIA, TIAR, T-cell intracellular antigen 1 and related protein.

Table 2a

Gene Amplification and Expression of *SRC1* in Human Tumors

Measurements	Methods	Amp. or Exp. Changes (n)	Molecular Association	Pathology Association	Refs
Breast cancer					
mRNA E	RT-PCR	lower in tumor (21)	ND	better tamoxifen response with high SRC-1	182
Protein O	IHC	high in 28% tumors (25)	ERβ+, SRC-2+	ND	86
Protein E	IHC	high in 29% tumors (52)	ND	LN+, recurrence tamoxifen resistance	83
Protein E	IHC	high in 25.7% tumors (70)	HER2+, PEA3+	recurrence, poor DFS	84
Protein E	IHC	high in 19% tumors (150)	ERβ-HER2+	recurrence, poor DFS	85
Endometrial Carcinoma					
Protein E	IHC	decrease in tumor (58)	ND	ND	121
mRNA E	qRT-PCR	increase in tumor (30)	ND	ND	120
Meningioma					
Protein E	WB, IHC	high in 81% tumors (21)	PR+	ND	183
Ovarian cancer					
mRNA E	RT-PCR	no change in tumors (17)	ND	ND	184
Prostate cancer					
Protein E	IHC, WB	high in recurrent PCa (8)	ND	high tumor grade	110
mRNA E	RT-PCR	high in high grade cancer (20)	ND	high tumor grade	111
Protein E	IHC	high in high grade tumors (500)	ND	high Gleason score	109
Mutation	sequencing	mutated in 1% tumors (81)	Val156Ile	ND	108
Gene A	FISH	in 2.8% tumors (70)	ND	ND	108
Protein E	IHC	high in 48% tumors (254)	more nuclear SRC-1	androgen resistance	108
mRNA E	qRT-PCR	ND (148)	ND	no significant correlation	112

Amp. or A, amplification; O, overexpression; Exp. Or E, expression; DFS, disease-free survival; n, number of samples; refs, references; LN+, lymph node positive metastasis; ISH, in situ hybridization; NB, Northern blot; SB, Southern blot; IHC, immunohistochemistry; WB, Western blot; FISH, fluorescence in situ hybridization; CGH, comparative genomic hybridization; ND, not determined.

Table 2b

Gene Amplification and Expression of *SRC2* in Human Tumors

Measurements	Methods	Amp. or Exp. Changes (n)	Molecular Association	Pathology Association	Refs
Breast cancer					
Protein E	IHC	no change (25)	SRC-1+	LN+	86
mRNA E	qRT-PCR	ND (99, ER+)	PR+, high cyclin D1	ND	96
Endometrial Carcinoma					
mRNA E	qRT-PCR	increase in carcinomas (30)	ND	ND	120
Meningioma					
Protein E	WB, IHC	high in76% samples (21)	PR+	ND	183
Ovarian cancer					
mRNA E	RT-PCR	no change (17)	ND	ND	184
Prostate cancer					
Protein E	IHC, WB	high in high grade tumors (16)	ND	high tumor grade	110
Protein E	IHC	variable (518)	ND	recurrence & proliferation	114
mRNA E	qRT-PCR	ND (148)	ND	no significant correlation	112

Amp. or A, amplification; O, overexpression; Exp. Or E, expression; DFS, disease-free survival; n, number of samples; refs, references; LN+, lymph node positive metastasis; ISH, in situ hybridization; NB, Northern blot; SB, Southern blot; IHC, immunohistochemistry; WB, Western blot; FISH, fluorescence in situ hybridization; CGH, comparative genomic hybridization; ND, not determined.

Table 2c

Gene Amplification and Expression of *SRC3* in Human Tumors

Measurements	Methods	Amp. or Exp. Changes (n)	Molecular Association	Pathology Association	Refs
Breast cancer					
Gene A	FISH	in 9.5% tumors (105)	ND	ND	11
mRNA O	ISH	high in 64% tumors (75)	ND	big tumor size	11
Gene A	SB	in 4.8% tumors (1157)	ER+, PR+, *MDM2* & *FGFR1* A	big tumor size	97
mRNA O	ISH	high in 31% tumors (83)	ER−, PR−, p53+, HER2+	high tumor grade	51
Gene A	PCR	no change (127)	ND	ND	99
mRNA O	RT-PCR	high in 13% tumors (23)	ND	ND	99
Protein O	IHC	high in 9.8% tumors (41)	ND	ND	87
Protein E	WB	high in 25% tumors (316 mix)	HER2+, PR+	high proliferation	
		high in 25% (119 no treat)	ND	better DFS	
		high in 25% (187 Tam treat)	HER2+	worse DFS, Tam resistance	52
Protein O	IHC	high in 20% tumors (25)	CBP/p300	high tumor grade	86
mRNA	qRT-PCR	high in 31.6% tumors (38)	ND	poor DFS	98
mRNA E	qRT-PCR	ND (99 ER+)	HER2+	ND	96
Protein E	IHC	high in 73.8% tumors (560)	MMP2/9+, PEA3+	ND	88
Colorectal Cancer					
Gene A	FISH	in 10% samples (85)	ND	ND	119
Protein O	IHC	high in 35% samples (85)	p53+, DNA aneuploidy	higher tumor grade	119
Gene A	CGH	in 32% samples (22)	ND	ND	185
Endometrial Carcinoma					
Gene A	PCR	no change (30)	ND	ND	99
mRNA O	RT-PCR	high in 17% samples (30)	ND	ND	99
mRNA E	qRT-PCR	increase in carcinomas (30)	ND	ND	120
Protein E	IHC	increase in 97% samples (84)	nuclear ER+, PRB+	poor prognosis	122
Esophageal squamous cell carcinoma					

Measurements	Methods	Amp. or Exp. Changes (n)	Molecular Association	Pathology Association	Refs
Gene A	SB, FISH	in 4.9% carcinomas (41)	20q A	metastasis, poor prognosis	186
Gene A	FISH	in 13% carcinomas (221)	ND	ND	123
Protein O	IHC	high in 46% carcinomas (221)	ND	high proliferation	123
Gastric cancer					
Gene A	SB, FISH	in 7% cancer (72)	ND	ND	124
mRNA O	NB, RT-PCR	high in 40% cancer (72)	ND	metastasis, poor prognosis	124
Hepatocellular carcinoma (HCC)					
Gene A	FISH	in 23% primary HCC (35)	ND	ND	
		in 41% metastatic HCC (33)	ND	ND	
		in 60% recurrent HCC (17)	ND	poor prognosis	187
Meningioma					
Protein E	WB, IHC	high in 76% samples (21)	ND	ND	183
Oral squamous cell carcinoma					
Gene A	CGH	ND (13)	ND	LN+	188
Ovarian cancer					
Gene A	SB	in 7.4% samples (122)	ND	ND	97
Gene A	CGH, FISH	in 25% samples (24)	ER+	poor prognosis	189
mRNA E	RT-PCR	no change (17)	ND	ND	184
Protein O	IHC	in 64% high grade cancer (83)	ND	high tumor grade	125
Pancreatic cancer					
Gene A	FISH	in 37% samples (46)	ND	ND	126
mRNA, Protein O	ISH, IHC	high in 65% samples (78)	ND	cancer progression	126
Prostate cancer					
mRNA, protein O	ISH, IHC	high in 38% samples (37)	ND	high tumor grade, poor DFS	115
Protein O	IHC	high in advanced cancer (480)	PSA recurrence, high pAKT	high proliferation	116

Amp. or A, amplification; O, overexpression; Exp. Or E, expression; DFS, disease-free survival; n, number of samples; refs, references; LN+, lymph node positive metastasis; ISH, in situ hybridization; NB, Northern blot; SB, Southern blot; IHC, immunohistochemistry; WB, Western blot; FISH, fluorescence in situ hybridization; CGH, comparative genomic hybridization; ND, not determined.