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Review

Steroid receptor coactivator-1: A versatile regulator and promising therapeutic target for breast cancer

Yanlei Zhang[a,b,1], Chenyang Duan[a,c,1], Chen Bian[a], Ying Xiong[a], Jiqiang Zhang[a,*]

[a] Department of Neurobiology, Chongqing Key Laboratory of Neurobiology, Third Military Medical University, Chongqing 400038, China
[b] Company Ten of Cadet Brigade, Third Military Medical University, Chongqing 400038, China
[c] Company Five of Cadet Brigade, Third Military Medical University, Chongqing 400038, China

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ABSTRACT

Breast cancer is the leading cause of cancer death for women worldwide. Various therapeutic approaches have been proposed, among which endocrine therapy has recently become popular due to the high sensitivity of breast tissues to steroids such as estrogens and progesterone. The underlying mechanisms of steroid regulation in breast cancer cell proliferation, invasiveness, metastasis and endocrine resistance, however, remain largely unknown. Steroid receptor coactivator-1 (SRC-1) has attracted much attention because it is an important co-regulator and plays a pivotal role in modulating the transcriptional activities of steroid nuclear receptors. Accumulated research has established a strong correlation between SRC-1 and the pathological progression or disease-related features of breast cancer, which supports its potential as a target for specific therapeutic intervention in the clinical management of breast cancer. In addition, a diverse group of downstream molecules have also been shown to participate in various functional pathways related to SRC-1-associated regulation of breast cancer. These downstream molecules are also considered promising therapeutic targets, providing additional options for targeted treatments. In this review, the expression of SRC-1 in breast cancer and the close relationships between SRC-1 and the cell proliferation, invasiveness, metastasis and endocrine resistance of breast cancer will be discussed, followed by a brief summary of its putative functional mechanisms with an emphasis on the potential therapeutic role of SRC-1.

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1. Introduction

Breast cancer is one of the most common malignant cancers for women and is reported to cause more than 500,000 deaths per year [1]. The mechanisms underlying the cell proliferation, invasion and metastasis of breast cancer are not yet clear. Because breast

* Corresponding author at: 30# Gaotanyan ST, Department of Neurobiology, Third Military Medical University, Chongqing 400038, China. Tel.: +86 23 68752232; fax: +86 23 68752232.
E-mail address: zhangjqtmmu@yahoo.com (J. Zhang).
[1] These authors contributed equally.

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cancer is steroid-sensitive [2–4], great efforts have been made to explore the use of steroids (such as estrogens) or the nuclear receptors of steroids (such as the estrogen receptors (ER) α and ER-β) as endocrine therapy targets [5]. Selective ER modulators (such as tamoxifen) and aromatase inhibitors (such as anastrozole or letrozole) are the two major endocrine drugs [6,7] that have already been applied as treatments for breast cancer. Tamoxifen is often given to patients with early-stage or metastatic breast cancer; it functions well in ER-positive breast cancers but has no effect on ER-negative breast cancers [7]. Aromatase inhibitors have been demonstrated to be superior to tamoxifen in both efficiency and toxicity and are usually administered in hormone-dependent breast cancer patients [8]. Unfortunately, both of these therapies are not always effective even cause serious side effects under some conditions. For example, aromatase inhibitors administration could not prevent tumour recurrence frequently [6]; tamoxifen may cause cognitive deficiency because estrogens have been shown to target brain regions that related to learning and memory as well as cognitive behavior [9]; it could also be estrogenic instead of antiestrogenic [10] thus increase the risk of endometrial cancers and thrombosis [7,11].

It has been established that the transcriptional activity of nuclear steroid receptors requires their coactivators, among which the p160 steroid receptor coactivator (SRCs) family has been widely studied in recent years. This family contains three members: SRC-1, -2 and -3. They share overall 50–55% sequence similarity and 43–48% sequence identity; all of them have 5 domains and the relatively conserved central region contains three LXXLL (L, leucine; X, any amino acid) motifs which is responsible for interaction with ligand-bound nuclear receptors (NRs); distinct LXXLL motifs and contextual sequences exhibit differential binding affinity for different NRs [12]. Accumulated studies have indicated the different but important roles of SRC-1, SRC-2 and SRC-3 respectively in regulating not only a range of physiological activities but also many pathological processes [13,14]. For instance, SRC-1 is suggested to play important roles in the physiology of the central nervous system such as the synaptic plasticity, as suggested in our previous studies [15–19], SRC-2 is demonstrated to function mainly in the metabolism-related events, and SRC-3 is validated to be a possible biomarker for many kinds of cancers including breast cancer, prostatic cancer [12,20]. SRC-1 was first cloned by Onate et al. [21] and is the auxiliary activation factor for many types of nuclear receptors [22]. SRC-1 has since been demonstrated to interact with steroid receptors in a steroid-dependent way, thereby initiating and promoting their regulation in the transcription of targeted genes [23,24]. To date, strong correlations between SRC-1 and the development, progression and even disease-free survival of breast cancer have been identified [25,26]. In this review, the versatile roles of SRC-1 in regulating the cell proliferation, metastasis and endocrine resistance of breast cancer will be highlighted, followed by a brief summary of its multiple underlying signalling pathways.

2. Expression of SRC-1 in breast cancer

The development of a normal mammary gland is highly dependent upon the regulation of steroids, and SRC-1 has been established to have low expression in normal mammary glands, but plays important roles in the elongation, branching and density of the normal mammary duct [14]. Decreased expression of SRC-1 is reported to give rise to a reduced ductal density and significantly less ductal branch occupation in the fat pad area [14] as well as decreased number and size of alveoli [14,27,28], suggesting SRC-1 is necessary for the development of normal alveoli following pregnancy.

Berns et al. reported high levels of SRC-1 mRNA in normal breast tissue [29], but later studies in which the protein level of SRC-1 was investigated indicated that SRC-1 protein was very low in normal mammary gland ductal epithelial cells [14,30] and were dramatically increased by approximately 19–29% in breast cancers [31,32]. The abnormal protein expression of SRC-1 has also been correlated with many molecular features and pathological events of breast cancer [13,14,31,33]. For example, the increased SRC-1 protein is correlated with breast cancer cell proliferation, metastasis, human epithelial receptor 2 (HER2) positivity, tumour grading, disease-free interval [31–34], which will be discussed in more detail in the following sections. Interestingly, one study showed that in ER negative breast cancers, SRC-1 was linked to early relapse and death [13]. Another study also reported that SRC-1 was negatively associated with disease-free survival, positively correlated with HER2 expression and inversely associated with ER-β;, which has been identified as a marker for increased disease-free survival [35].

Therefore, the level of SRC-1 in breast tissue may serve as a potential diagnostic factor because it is low under physiological conditions but dramatically increases in breast cancer tissues. Currently, few studies address the mRNA expression of SRC-1 in normal or cancerous breast tissue, so more work is needed to elucidate the correlations between the expression levels of SRC-1 and pathological features such as tumour type, grading, metastasis status, etc. What's more, the combined diagnostic potentials of the expression patterns of several factors such as SRC-1, HER2, ER-α and ER-β need further investigation.

3. SRC-1 in the proliferation of breast cancer cells

The activity of steroids such as 17β;-estradiol (E2), their receptors and their receptor coactivators in cancer cell growth and proliferation have been explored extensively in previous studies [2–4]. These have demonstrated that SRC-1-mediated regulation of breast cancer cell proliferation may occur through various mechanisms as shown in Fig. 1. Firstly, SRC-1 has been shown to promote breast cancer cell proliferation by stimulating the function of ER-α [36], which accounts for the aberrant cell proliferation in about two-thirds of breast cancer cases [37]. The SRC-1/ER-α complex is supposed to potentiate E2-stimulated MCF-7 cell growth by enhancing the transcriptional activation of many exogenous and endogenous E2-responsive genes[23,38], including cyclin D1a and Mucin1 (MUC1), which are both overexpressed in breast cancer and involved in the SRC-1/ER-α-related proliferation-enhancing pathways [26,39]. This complex also promotes cancer cell survival by suppressing TNF-α-induced apoptosis [38]. Secondly, Kishimoto et al. identified an autocrine mechanism of SRC-1-mediated estrogen-induced cancer cell proliferation [40]. SRC-1 was shown to mediate cancer cell proliferation through the autocrine activity of the growth-stimulatory cytokine stromal cell-derived factor 1 (SDF-1/CXCR12), which is a novel target of ER-α and PEA3 action in human breast cancer cells [41,42]. Its receptor, CXCR4, is supposed to be regulated by PEA3 [43]. Thirdly, Myc is one of the most important proto-oncogenes, which is sufficient for regulating cancer cell proliferation [44] and SRC-1 was shown to coactivate the expression of Myc through Ets-2 [6,14,31]. In addition, SRC-1 has also been shown to be involved in the signal transducer and activator of transcription 3 (STAT3) signalling pathway, suggesting its potential involvement in leptin-stimulated breast cancer cell proliferation [45].

Therefore, SRC-1 may play important roles in regulating the proliferation of breast cancer cells through various functional pathways. As shown in Fig. 1, these results support the therapeutic potential of SRC-1 to function as a novel target for breast cancer anti-proliferation therapy.