Staying the Distance: Avoiding the Proteasomal Trap

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There are a multitude of nuclear receptor coactivators, and as a result, individual constituents of activation complexes are often overlooked when studying the specific actions of hormone signaling pathways. Specificity is typically associated with the receptor and its cognate ligand. However, SRC-3 has distinguished itself by persistent association with cell growth. In the February 29 issue of *Molecular Cell*, Yi et al. demonstrate that estrogen-induced posttranslational modulation of SRC-3 by atypical PKC shields it from proteasomal degradation, facilitating increased estrogenic gene activity. This process may have important implications in different types of hormone-sensitive tumors, particularly breast cancer.

Breast cancer is the most commonly diagnosed cancer among women; in 2008, some 182,460 new cases are expected, and from these, 40,480 deaths are estimated (American Cancer Society, 2008). As with any complex disease, development of new therapies depends on knowledge of the underlying source of the problem. The relationship of the estrogen receptor (ER), a member of the nuclear hormone receptor (NR) family, with breast cancer has been a focus of these studies. Since many breast tumors proliferate in response to the female sex steroid estrogen, current treatment includes various forms of endocrine therapy. The most commonly used form of treatment is tamoxifen, a selective ER modulator (SERM) that competitively inhibits estradiol binding to the ER. The predominance of studies on the actions of ER in breast cancer often overlooks the importance of nuclear receptor coactivators as a major determinate of ER transcriptional activity in breast cancer.

The nuclear receptor coactivator SRC-3 was simultaneously cloned by several groups in 1997 as a CBP-interacting protein (p/CIP; Torchia et al., 1997), a nuclear receptor cofactor for activated retinoid and thyroid hormone receptors (ACTR; Chen et al., 1997), and as it relates to this article amplified in breast cancer (AIB1; Anzick et al., 1997). Subsequent studies have shown that SRC-3 is an atypical histone acetyltransferase (HAT) (Chen et al., 1999) whose increased expression is associated with hormone-sensitive tumors such as prostate and ovarian cancer in addition to hormone-independent cancers such as pancreatic and gastric cancers. It is a member of the p160 class of nuclear receptor coactivator proteins that associate with NRs in a ligand-dependent manner to promote their transcriptional activation of target genes. While nuclear receptor cofactors like SRC-3 are generally thought to facilitate the actions of NR activity, growing evidence shows that relative cofactor concentration can proportionately drive receptor function. Thus, it may not be surprising that cofactor overexpression might directly contribute to disease, pathology, and outcome. How might overexpression or excess protein be achieved? In the case of the nuclear receptor coactivator PGC-1a, its levels are dramatically induced from a "bottom-up" path involving enhanced transcription-translation producing more protein (Puigserver and Spiegelman, 2003). In contrast, in the current article the authors describe a "top-down" control pathway in which posttranslational modifications of SRC-3 can shield it from the jaws of the proteasome, leading to increased protein accumulation and increased activity of downstream targets genes such as those controlling cell growth (Yi et al., 2008).

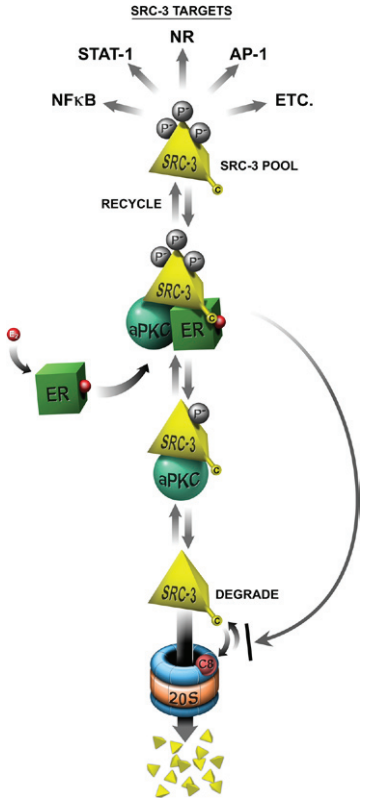

Figure 1. ER-Dependent Resistance of SRC-3 Degradation via aPKC Activity
Schematic pathway of how inhibition of SRC-3 proteasomal degradation via aPKC-mediated phosphorylation in an ER-dependent manner leads to an increase in total cellular levels of SRC-3.

Phosphorylation can be a double-edged sword, as previous work has shown that both p38 MAP kinase and GSK-3 can trigger selective degradation of SRC-3 through either the 26S or the REGγ-mediated proteasome (Wu et al., 2007). In the present study, Yi and colleagues show that alternative phos-

phorylation of the carboxy-terminal tail by the atypical PKC (aPKC) prevents 20S proteasomal degradation of SRC-3, negating the effects of p38 MAP kinase and GSK-3 activity. The net result of aPKC phosphorylation is the cellular accumulation of the coactivator and enhanced ER-dependent gene transcription. Interestingly, other NRs such as the progesterone receptor do not exhibit a similar ability to trigger phosphorylation of SRC-3 by aPKC, highlighting the relevance of this mechanism to estrogen-dependent breast cancer cell growth. The authors show that the normal degradation of SRC-3 involves an initial interaction with the C8 alpha component of the 20S proteasome. However, when hyperphosphorylated by aPKC, SRC-3 undergoes a conformational change, exposing a negatively charged sequence that inhibits the interaction with C8 via electrostatic repulsion, effectively shielding it from the proteasome and resulting in a net increase in the cellular pool of this cofactor.

The relevance of this finding to breast cancer pathology is strengthened by the observation that SRC-3 phosphorylation by aPKC is promoted by hormone-activated ER. This leads to a proposal that estradiol binding to ER allows the receptor to associate and stabilize the SRC-3-aPKC dimer (Figure 1). The presumptive trimeric complex facilitates SRC-3 phosphorylation, which in turn increases transcription of ER of target genes. Interestingly, overexpression of aPKC has been observed in a number of cancers (Regala et al., 2005), which may provide an independent means to enhance SRC-3 pool size and ER transcription. Beyond NRs, SRC-3 has been shown to be a coactivator of other transcriptional networks, including activator protein-1 (AP-1), nuclear factor-κB (NFκB), signal transducer and activator of transcription (STAT), and E2F1, all of which have been associated with cell growth and cancer (Liao et al., 2002). Thus, the work presented by Yi and colleagues provides us with a new model of how posttranslation modifications of a NR coactivator may promote cancer while offering a new therapeutic target to exploit in its treatment.

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Learning the ABCs of Melanoma-Initiating Cells

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Tumor stem or initiating cells have been proposed to exist for melanoma. Stem-like cells have been propagated from melanoma cell lines and specimens. Additionally, classical stem cell markers, including ABCG2 and CD133, have been identified in clinical melanomas. However, definitive markers for the purification and further characterization of melanoma-initiating cells remained elusive. Recently, Schatton et al. provided solid evidence that the doxorubicin-resistant ATP-binding cassette transporter ABCB5 marks primitive cells capable of recapitulating melanomas in xenotransplantation models. The identification of melanoma-initiating cells has far-reaching implications, as new therapeutic strategies can be envisioned that specifically target these cells.

A cancer stem cell hierarchy has been suggested to exist for melanomas in which primitive self-renewing melanoma cells, capable of initiating tumorigenesis, give rise to rapidly proliferating, more differentiated, and tumorigenically exhausted cells that constitute the bulk tumor population. Stem-like cells have been propagated from both cultured melanoma cells and fresh clinical specimens as nonadherent spheres in stem cell-supportive media, similar to mammo- and neurospheres, that could self-renew, differentiate into various mesenchymal lineages, and initiate tumors in xenotransplantation models with small cell number (Fang et al., 2005). Furthermore, stem cell properties, including side population, and stem cell makers, including ABCG2, CD133, and nestin, have been identified in melanomas (Dou et al., 2007; Grichnik et al., 2006; Klein et al., 2007; Monzani et al., 2007). Despite this suggestive evidence, in depth in