Molecular Cancer

BioMed Central

Review

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The roles of sex steroid receptor coregulators in cancer

Xiuhua Gao, Brian W Loggie and Zafar Nawaz*

Address: CUMC-Cancer Center, Creighton University, 2500 California Plaza, Omaha, NE 68178, USA

E-mail: Xiuhua Gao - xiuhuagao@hotmail.com; Brian W Loggie - bloggie@creighton.edu; Zafar Nawaz* - znawaz@creighton.edu

*Corresponding author

Published: 14 November 2002

Molecular Cancer 2002, **1**:7

Received: 13 November 2002

Accepted: 14 November 2002

This article is available from: http://www.molecular-cancer.com/content/1/1/7

Keywords: nuclear receptors, steroid receptors, coregulators, coactivators, corepressors, cancer

Abstract

Sex steroid hormones, estrogen, progesterone and androgen, play pivotal roles in sex differentiation and development, and in reproductive functions and sexual behavior. Studies have shown that sex steroid hormones are the key regulators in the development and progression of endocrine-related cancers, especially the cancers of the reproductive tissues. The actions of estrogen, progesterone and androgen are mediated through their cognate intracellular receptor proteins, the estrogen receptors (ER), the progesterone receptors (PR) and the androgen receptor (AR), respectively. These receptors are members of the nuclear receptor (NR) superfamily, which function as transcription factors that regulate their target gene expression. Proper functioning of these steroid receptors maintains the normal responsiveness of the target tissues to the stimulations of the steroid hormones. This permits the normal development and function of reproductive tissues. It can be inferred that factors influencing the expression or function of steroid receptors will interfere with the normal development and function of the target tissues, and may induce pathological conditions, including cancers. In addition to the direct contact with the basal transcription machinery, nuclear receptors enhance or suppress transcription by recruiting an array of coactivators and corepressors, collectively named coregulators. Therefore, the mutation or aberrant expression of sex steroid receptor coregulators will affect the normal function of the sex steroid receptors and hence may participate in the development and progression of the cancers.

Introduction

The mammary gland, the ovary and the uterus in females, and the testis and the prostate gland in males are the main target tissues of sex steroid hormones including estrogen, progesterone, and androgen. Estrogen is important for the growth, differentiation and function of both female and male reproductive tissues [1,2], whereas progesterone is an essential regulator of the reproductive events associated with the establishment and maintenance of pregnancy, including ovulation, uterine and mammary gland development [3]. Androgen is involved in the development and physiological function of male accessory sex organs [4], and it is also indispensable for the normal development and function of female reproductive tissues. These hormones exert their functions in the target tissues through their specific intracellular receptors, the estrogen receptors (ER), the progesterone receptors (PR) and the androgen receptor (AR), which belong to the nuclear re-

ceptor (NR) superfamily and function as transcription factors to regulate the target gene expression [5]. The abnormal expression or function of these receptors has been implicated in tumors of reproductive organs in both genders. Furthermore, the development of resistance to hormonal replacement therapy for either breast or prostate cancers is also related to aberrant expression, mutation of the genes and abnormal functioning of the respective steroid receptors.

As members of the NR superfamily, the sex steroid receptors, ER, PR and AR, share the characteristic structure with other nuclear receptors (NRs): an amino-terminal activation, AF-1 (A/B domain); the DNA-binding domain (DBD) (C); a hinge region (D domain); and a carboxy-terminal ligand-binding domain (LBD) (E), which contains a second activation function, AF-2 [5]. In the absence of hormones, NR is sequestered in a non-productive form associated with heat shock proteins and other cellular chaperones. In this state, NR is inactive and unable to influence the transcription rate of its target gene promoters [5,6]. Upon binding with the cognate hormones, the receptors undergo a series of events, including conformational changes, dissociation from heat shock protein complexes, dimerization, phosphorylation, and nuclear translocation, which enables their binding to hormone-response elements (HREs) within the regulatory regions of target genes [5,6]. The binding of hormones to the HREs causes the recruitment of coactivators and basal transcription machinery, leading to the upregulation of target gene transcription.

Coactivators are factors that can interact with NRs in a ligand-dependent manner and enhance their transcriptional activity. Corepressors are factors that interact with NRs, either in the absence of hormone or in the presence of antihormone, and repress their transcriptional activity. Both types of coregulators are required for efficient modulation of target gene transcription by steroid hormones. Therefore, changes in the expression level and pattern of steroid receptor coactivators or corepressors, or mutations of their functional domains can affect the transcriptional activity of the steroid hormones and hence cause disorders of their target tissues. This review will summarize our current understanding about the roles that the coactivators and corepressors may play in the development and progression of cancers in both male and female reproductive tissues.

The SRC family

The SRC (steroid receptor coactivator) family is composed of three distinct but structurally and functionally related members, which are named SRC-1 (NcoA-1), SRC-2 (TIF2/GRIP1/NcoA-2), and SRC-3 (p/CIP/RAC3/ACTR/AIB1/TRAM-1), respectively [5]. Sequence analysis of SRC proteins identified a basic helix-loop-helix (bHLH) domain and two Per-Arnt-Sim (PAS) domains in the amino-terminal region, a centrally located receptor-interacting domain (RID) and a C-terminal transcriptional activation domain (AD). The bHLH/PAS domain is highly conserved among the SRC members and it serves as a DNA binding and protein dimerization motif in many transcription factors. Detailed analysis revealed three conserved LXXLL motifs (NR box) in the RID, which appear to contribute to the specificity of coactivator-receptor interaction. Histone acetyltransferase (HAT) activity was identified in the C-terminal region of SRC members and there also exist activation domains that can interact with the CREB-binding protein (CBP). The members of the SRC family interact with steroid receptors, ER, PR and AR, and enhance their transcriptional activation in a ligand-dependent manner [5].

SRC-1 was the first coactivator for the steroid receptor superfamily that was cloned and characterized [7]. SRC-1 is a common transcription mediator for nuclear receptors, functioning through its HAT activity and multiple interactions with agonist-bound receptors. SRC-1 exhibits a broad range of specificity in the coactivation of the hormone-dependent transactivation of nuclear receptors, including PR, ER, GR (glucocorticoid receptor), TR (thyroid hormone receptor), and AR. Targeted deletion of SRC-1 gene in mice has indicated that SRC-1 is required for efficient steroid hormone action in vivo; for estrogen and progesterone action in the uterus and mammary gland, and for androgen action in the prostate and testis [8].

The role of SRC-1 in the development or progression of cancers is not clear. Although it is an important coactivator for ER and PR, there have been no positive results showing that the expression of SRC-1 is altered in breast cancers or ovarian cancers. However, results from different groups indicated that SRC-1 is involved in the progression of prostate cancers. Using RT-PCR (reverse transcriptase-polymerase chain reaction), Fujimoto and colleagues found that the expression levels of SRC-1 were higher in higher grade prostate cancers or cancers with a poor response to endocrine therapy [9]. At the same time, Gregory *et al* reported that SRC-1 expression was elevated, together with the expression of AR, in recurrent prostate cancers [10]. Gregory *et al* found that SRC-2 is also overexpressed in recurrent prostate cancers. Overexpression of SRC-1 and SRC-2 confers on AR an increased sensitivity to the growth-stimulating effects of low androgen concentrations. This change may contribute to prostate cancer recurrence after androgen deprivation therapy.

SRC-3 is the most distinct among the three members of SRC family; it coactivates not only the nuclear receptors but also other unrelated transcription factors such as

those in the cAMP or cytokine pathways. Compared with the widespread expression of SRC-1 and SRC-2, expression of SRC-3 is restricted to few tissues, including the uterus, the mammary gland and the testis [11]. Disruption of SRC-3 gene in mice causes severe growth and reproductive defects, such as the retardation of mammary gland development [12]. Amplification and overexpression of SRC-3 in human breast and ovarian cancers have been observed [13–17]. Bautista *et al* reported that the AIB1 (SRC-3) amplification/overexpression was correlated with ER and PR positivity [14]. However, Bouras *et al* found that SRC-3 had an inverse correlation with steroid receptors, but a positive correlation with HER-2/Neu and p53 expression [17]. Despite of the conflicting results, the overexpression of SRC-3 in breast and ovarian tumors indicates that SRC-3 is an important factor in the tumorigenesis of the mammary gland and ovary. There is no clear evidence about the possible roles of SRC-3 in prostate tumor development and progression.

SRA/SRAP

The steroid receptor RNA activator (SRA) is a unique coactivator for steroid receptors, PR, ER, GR, and AR. Differing from the other coactivators, SRA was found to function as a RNA transcript instead of as a protein [18]. Besides, SRA existed in a ribonucleoprotein complex containing SRC-1 and it mediated transactivation through the AF-1 domain located at the N-terminal region of nuclear receptors, distinguishing it from the other coactivators [18].

SRA is expressed in normal and malignant human mammary tissues [15,19]. Compared with the adjacent normal region, elevated expression of SRA was found in breast tumors [15]. Although it is currently unknown whether the expression of SRA is correlated with that of PR or ER, the increase in the SRA levels in tumor cells may contribute to the altered ER/PR action, which is known to occur during breast tumorigenesis.

Recently, Kawashima *et al* reported the cloning and characterization of a novel steroid receptor coactivator from a rat prostate library [20]. The nucleotide sequence of this coactivator has 78.2% identity to that of human SRA, however, the cDNA of this coactivator can be transcribed into a functional protein and exerts its coactivation function as a protein instead of an RNA transcript [20]. Therefore, it was designated as steroid receptor activator protein, SRAP. Kawashima *et al* demonstrated that SRAP could enhance the transactivation activity of AR and GR in a ligand-dependent manner. The mRNA of SRAP was expressed in all the rat prostate cancer cell lines examined, while that of SRA was expressed in all the human prostate cancer cell lines. The expression level of SRA is higher in androgen-independent PC-3 cells compared with that of the androgen-dependent cell lines, DU-145 and LNCaP. Taken together, these results suggested that both SRA and SRAP play an important role in NR-mediated transcription in prostate cancer.

E6-AP/RPF1

E6-associated protein, E6-AP, and RPF1, the human homolog of yeast RSP5, are E3 ubiquitin-protein ligases that target proteins for degradation by the ubiquitin pathway. They are also characterized as coactivators of steroid receptors. It has been demonstrated by transient transfection assay that RPF1 and E6AP can potentiate the ligand-dependent transcriptional activity of PR, ER, AR, GR, and other NRs [21,22]. Furthermore, they also act synergistically to enhance the transactivation of NRs [22]. Additionally, the coactivation functions of E6-AP and RPF1 are not dependent on the E3 ubiquitin-protein ligase activity.

E6-AP is expressed in many tissues including the uterus, ovary, testis, prostate and mammary gland. It is important in the development and function of these tissues, since E6-AP null mutant mice exhibited defects in reproduction in both male and female mice [23].

The first evidence of a relationship between E6-AP and cancer was obtained from the study of a spontaneous mouse mammary tumorigenesis model. In this spontaneous model, E6-AP was overexpressed in mammary tumors when compared with normal tissues [24]. Recently, we examined the expression pattern of E6-AP in biopsy samples of human breast cancers. Our results showed that E6-AP expression was decreased in tumors in comparison to the adjacent normal tissues (Gao *et al*, unpublished data). In addition, the expression of E6-AP was inversely correlated with that of ER in breast tumors, and the decreased expression of E6-AP was stage-dependent. Interestingly, the decreased expression of E6-AP was also found in human prostate cancers (Gao *et al*, unpublished data). ER plays a major role in breast cancer development, and PR is also a target of estrogen. Thus, changes in the expression level of E6-AP, a coactivator for ER and PR, might interfere with the normal functioning of ER and PR, hence participating in the formation and progression of breast tumors. In a similar way, the altered expression of E6-AP might influence the normal functioning of AR, which plays a major role in the progression of prostate cancers.

ASC-2/TRBP/AIB3

ASC-2 (the nuclear protein-activating signal cointegrator-2), also called AIB3 (the amplified in breast cancer 3) and TRBP (TR-binding protein), has recently been characterized as a NR coactivator [25]. ASC-2 interacted with NRs, such as retinoid acid receptor (RAR), TR, ER, and GR, and stimulated the ligand-dependent and AF2-dependent transactivation of the NRs either alone or in conjunction with CREB-binding protein (CBP)/p300 and SRC-1. Sub-

sequent study showed that ASC-2 also interacted with SRF (the serum response factor), AP-1 (the activating protein-1), NF-κB (the nuclear factor-κB), and potentiated transactivation by these mitogenic transcription factors [26]. This suggests that ASC-2 is a multifunctional transcription integrator molecule.

ASC-2 is likely involved in the tumorigenesis of mammary gland, because it is amplified and overexpressed in human breast cancer specimens as well as in all the human breast cancer cell lines examined. Moreover, it may also regulate cellular proliferation or tumorigenesis by the direct interaction with SRF, AP-1 and NFκB.

L7/SPA

L7/SPA, L7/switch protein for antagonists, is a 27 kDa protein containing a basic leucine zipper domain. L7/SPA is an antagonist specific transcriptional coactivator because it can only potentiate the partial agonist activity of some antagonists, including tamoxifen and RU486, but has no effect on the agonist-mediated transcription [27]. The study by Graham *et al* indicated that the relative levels of the coactivator, L7/SPA, vs. the corepressors, which suppress the partial agonist activity of tamoxifen or RU486, might determine whether the agonist or antagonist effects of these mixed antagonists predominate in a tissue or tumor [28]. This unique property of L7/SPA could partially explain the development of resistance to hormone therapy for breast cancers.

ARAs

ARAs, androgen receptor-associated proteins, is a group of factors that can bind to AR and modulate its transcriptional activity. Based on their molecular weights, these factors were named ARA70, ARA160, ARA54, ARA55, ARA267 and ARA24.

ARA70, which has a molecular weight of 70-kDa, is also named as RFG (RET fused gene) and ELE1. ARA70 was first described as an AR-specific coactivator by Chang's group in 1996 [29]. In that report, ARA70 was demonstrated as a factor, which specifically interacts with AR and enhances the transcriptional activity of AR in response to the stimulation of androgens, including testosterone and dihydrotestosterone, but not the antiandrogen, hydroflutamide (HF). Later, it was reported that ARA70 could also interact with and facilitate the agonist activity of antiandrogens, including cyproterone (CPA), HF, and bicalutamide (casodex) [30]. Recent studies by other groups showed that ARA70 was not a specific coactivator for AR; it could also interact with PR or GR [31,32]. However, studies on the expression patterns of ARA70 in different cell lines and human cancer samples showed that the expression of ARA70 was decreased in prostate cancer [31,33–35] and breast cancer, [36] while it was increased in ovarian cancers. In breast, loss of ARA70 protein expression was found in 60% of HER2 positive breast cancers, while only 33% of HER2 negative breast cancer samples lost the expression [36]. Since androgen plays an inhibitory role for breast cancer cell growth, and HER2 stimulates the growth of breast cancers, loss of the expression of AR and/or ARA70 in breast might confer a growth advantage to these cells. In prostate, ARA70 mRNA is highly expressed in the normal epithelial cells, while benign prostatic hyperplasic and cancer cell lines express either lower or no ARA70 [36]. Methylation might be responsible for the lack of expression of ARA70 in some prostate cancer cells such as DU145 [36]. The expression of ARA70 in prostate cancer cells seems to be regulated by both ER and AR, since the prostate cancer cell line, PC-3, responded to estrogen/androgen and their respective antagonists differently in the parental PC-3 cells (AR-negative) and its derived AR-positive cells.

Other members of the ARA group, such as ARA54, ARA55, ARA24, ARA160, and ARA267 were also implicated in prostate tumors [35,37–40]. The expression of these coactivators was more or less altered in human prostate cancer cell lines or biopsy samples. However, the exact roles of these factors in prostate tumorigenesis need to be determined.

The PIAS family

The PIAS (protein inhibitor of activated signal transducer and activator of transcription) family is composed of a group of proteins that share a high sequence homology [41]. The first member of this family, PIAS1, was characterized as a coactivator for AR [42]. Through its N-terminal LXXLL motifs, PIAS1 interacted with and coactivated the AR transcriptional activity in a ligand-dependent manner [42]. Besides, PIAS1 could also modulate the activities of steroid receptors such as GR, PR and ER [42,43]. PIAS1 was expressed predominantly in the testis [42]. Furthermore, overexpression of PIAS1 was found in 33% of the prostate cancer samples examined [35]. These data suggested a possible role that PIAS1 may play in normal or cancer development of the testis or prostate.

Another important member of the PIAS family is called PIASxα or ARIP3 (AR-interacting protein 3). PIASxα/ARIP3 is similar to PIAS1 in that it is also expressed predominantly in the testis, and functions as a coactivator for AR [43,44].

SNURF

The small nuclear RING finger protein, SNURF, was identified in a yeast two-hybrid screening using the DBD of AR as a bait [45]. SNURF interacted with AR, GR and PR, and enhanced their transcriptional activity in a ligand-dependent fashion. It also potentiated the basal transcrip-

tion from steroid-regulated promoters [45]. SNURF is a nuclear protein. The expression of SNURF was relatively high in the brain, but low in the testis, prostate, seminal vesicles, spleen and kidney [45]. Moreover, the nuclear localization signal (NLS) in SNURF was found to be able to facilitate the nuclear import and export of AR [46], which is important for normal functioning of AR transactivation.

BRCA1

BRCA1 is a breast cancer susceptibility gene, and its inherited mutations are correlated with an increased risk of breast and ovarian cancers [47]. The role of BRCA1 in cancer development is quite complex. On one hand, BRCA1 was shown to coactivate p53, modulate p300/CBP expression, and function as a ligand-independent corepressor for ER, PR, and AR [48–50]; on the other hand, it was shown that it could enhance the ligand-dependent AR transactivation in both breast and prostate cancer cell lines, especially in the presence of exogenous SRC family members [51]. These results are somewhat controversial regarding the influence of BRCA1 on AR activity. ER and PR play key roles in breast cancer development and progression, and AR signaling in the breast has protective effect. Thus, it is reasonable to speculate that the normal expression of BRCA1 probably protect the breast from tumorigenesis by suppressing the ER and PR signaling pathway and promoting the AR activity. Mutation of the BRCA1 gene, therefore, increases the risk of developing cancer.

In a recent study by Ko *et al*. a genomic transcript, GT198, that mapped to the human breast cancer susceptibility locus (17q12-q21), was characterized as a coactivator for nuclear receptors such as AR, ER, PR, GR, etc [52]. GT198 has a tissue-specific expression pattern; it is expressed highly in testis, moderately in thymus, spleen, and pituitary, and hardly detected in other tissues. The role of this novel coactivator in cancers of testis or breast needs to be explored.

CBP/p300

CREB-binding protein (CBP) was initially characterized as a coactivator required for efficient transactivation of cAMP-response element-binding protein. p300 was first identified as a coactivator of the adenovirus E1A oncoprotein. CBP and p300 share many functional properties. Both of them function as coactivators for multiple NRs as well as p53 and NF-kB; both possess intrinsic HAT activity and both can recruit HAT and p/CAF (CBP/p300-associated factor) [5]. Besides, CBP/p300 interacts with members of SRC family and synergizes with SRC-1 in the transactivation of ER and PR [53]. Based on its wide expression and multiple functions, it is speculated that CBP/p300 might participate in the process of tumor initiation and progression.

N-CoR/SMRT

N-CoR and SMRT are both corepressors of numerous transcription factors, including steroid hormone receptors. Both N-CoR and SMRT interact with the nuclear receptors through the RIDs located in the C-terminal portion of the proteins, while their transcriptional repression domains were mapped to the N-termini [54]. N-CoR/SMRT also associates with HDAC3 (histone deacetylase 3) in large protein complexes, which is an important pathway for transcriptional repression. Corepressors N-CoR and SMRT interact with the NRs either in the absence of agonists (in the case of TR and RAR), or in the presence of antagonists (in the case of steroid receptors) [54]. As mentioned above, corepressors, N-CoR and SMRT, can suppress the partial agonist activity of antagonists, counteracting the effects of L7/SPA. The alteration of the expression of these corepressors changes the balance of corepressors to coactivators that are bound to the transcription complex via the antagonist-occupied steroid receptors. This might determine whether the outcome is inhibitory or stimulatory, and therefore determine whether tamoxifen-resistance will occur or not.

Other coregulators

In addition to the above-mentioned coactivators and corepressors, there are many other factors that have been characterized as sex steroid receptor coregulators. These include HMG-1/2 (the chromatin high-mobility group protein-1, 2), TIP60 (Tat-interacting protein), PNRC1/2 (proline-rich nuclear receptor coregulatory protein-1, 2), Cdc25B, Uba3 (ubiquitin-activating enzyme 3), and RTA (repressor of tamoxifen transcriptional activity) [55–60]. At present, it is not clear whether these coregulators are involved in the development of cancers.

Conclusion

Steroid receptors activate their target gene transcription in response to the hormonal stimulus. Their transactivation activities are modulated by coregulators (coactivators and corepressors). Different coregulators exert their actions through different mechanisms. Involvement of coregulators in the development and progression of cancers is complex. Most of the steroid receptor coactivators and corepressors identified so far are widely expressed. They usually can modulate the transactivation of multiple receptors. On the other hand, the transactivation function of a single nuclear receptor in certain tissues is usually regulated by multiple coregulators. Much evidence supports the importance of coregulators in tumorigensis and the development of hormone-resistance in breast or prostate cancers. The understanding of the mechanisms of the actions of these coregulators will be helpful for the development of new cancer therapies.

Authors' contributions

XG and BWL drafted the manuscript and ZN supervised and performed the final editing. All authors read and approved the final manuscript.

Acknowledgements

This work was supported in part by grants to Dr. Zafar Nawaz (NIH DK56833, NIH DK60907, DOD DAMD17-99-1-9075, and DOD DAMD17-00-1-0142). Xiuhua Gao is a recipient of the DOD Breast Cancer Postdoctoral Research Fellowship (DAMD17-02-1-0281).

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