Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Deep Insight Section

The roles of SRA1 gene in breast cancer

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Published in Atlas Database: March 2010

Online updated version : http://AtlasGeneticsOncology.org/Deep/SRA1inCancerID20085.html
DOI: 10.4267/2042/44929

Abstract

The Steroid receptor RNA activator (SRA) gene has been implicated in estrogen receptor signaling pathway. First identified as a RNA coregulator, SRA had been shown to increase steroid receptor activity. SRA RNA expression is altered during breast tumorigenesis and its molecular role in underscoring these events has been suggested. The subsequent identification of molecules capable of binding SRA, including RNA helicase p68, SRA stem-loop interacting RNA binding protein (SLIRP), and steroidogenic factor 1 (SF1) indicates SRA function is not exclusively limited to modulate steroid receptor activity. A recent genome-wide expression analysis by depleting SRA in cancer cells has further expanded our understanding of a broader biological role played by SRA. In addition, several RNA isoforms have been found to encode an endogenous protein (SRAP), which is well conserved among Chordata. Interestingly, SRAP also modulates steroid receptor activity and functions as a co-regulator in estrogen receptor signaling. The recent observation that a higher expression of SRAP protein is associated with poorer survival in breast cancer patients treated with tamoxifen, highlights the potential relevance of this protein in cancer. Together, the SRA1 gene encodes both functional RNA and protein (SRAP) products, making it a unique member amongst the growing population of steroid receptor co-regulators.

1. Introduction

It is now quite apparent that the end results of Estrogen Receptor (ER) mediated signaling is not simply limited to ER status and/or the presence of its naturally occurring ligand estridiol. In addition to the two known estrogen receptors, ERα and ERβ, ERs-mediated gene transcription also requires transcription co-regulators, which form complexes with estrogen receptors through protein-protein interactions followed by dynamic recruitment to specific gene promoters. Based on the outcomes of their regulations, co-regulators are categorized as either co-activators or co-repressors if they either promote or prevent gene transcription respectively. These complexes regulate the assembly and activity of the transcription initiation complex through chromatin remodeling (McKenna et al., 1999; Jenuwein and Allis, 2001).

Since the characterization of the first co-regulator, the steroid receptor co-activator 1 (SRC-1), this list of factors has grown significantly to now include over 300 co-regulators (Lonard and O'Malley, 2007). One particularly interesting member within this family was identified by Lanz et al. in 1999, as it was found not to act as a protein molecule but as a functional RNA. This nuclear co-regulator was therefore named Steroid receptor RNA activator (SRA) (Lanz et al., 1999).

2. Steroid Receptor RNA Activator (SRA)

2.1 Discovery of SRA, an RNA Co-activator

In order to identify new potential co-regulators interacting with AF-1 domain of the progesterone receptor (PR), Lanz screened a human B-lymphocyte library using AF-1 domain as bait in a yeast-two-hybrid assay (Lanz et al., 1999). They identified a new clone, they called SRA, for steroid receptor RNA activator. This cDNA was unable to encode a protein, but was required for the growth of the yeast colony. Further experiment confirmed that the potential co-activation role of SRA on PR was mediated through a RNA transcript rather than any protein product.

2.2 Core sequence of SRA and predicted functional region

In the incipient SRA study, a core sequence spanning SRA exon 2 to exon 5 was found to be necessary and sufficient for co-activation function of SRA RNA (Figure 1, Lanz et al., 1999). Several predicted secondary RNA structural motifs are distributed throughout this core sequence, and are believed to form the functional structures that impart SRA activities. Site-directed mutagenesis experiment revealed six secondary structural motifs (STR1, 7, 9, 10, 11, 12) that independently participate in PR co-activation by SRA (Lanz et al., 2002). It was found that silent mutations in both SRT1 and STR7 of SRA could decrease by more than 80% co-activation SRA's function (Lanz et al., 1999).

2.3 Effect of SRA RNA on ERα and ERβ signaling

Several research groups have now confirmed that SRA is able to increase estradiol induced gene transcription by both full length ERs subtypes (Watanabe et al., 2001; Deblois and Giguère, 2003; Coleman et al., 2004; Klinge et al., 2004). SRA RNA has been shown to co-activate the action of the AF-2 domain of both ERα and ERβ in a ligand-dependent manner on some, but not all estrogen receptor element (ERE) as measure through luciferase reporters assay (Deblois and Giguère, 2003; Coleman et al., 2004).

Interestingly, SRA can also enhance AF-1 domain of ERα but not ERβ in a ligand-independent manner (Coleman et al., 2004; Deblois and Giguère, 2003). Overall, data suggest that the action of the two estrogen receptors are differentially regulated by SRA and SRA regulation of a given receptor is also specific of a given ERE sequence (Leygue, 2007).

2.4 Emerging mechanisms of SRA RNA action

Several studies have been published discussing the mechanism of SRA RNA action (Leygue, 2007).

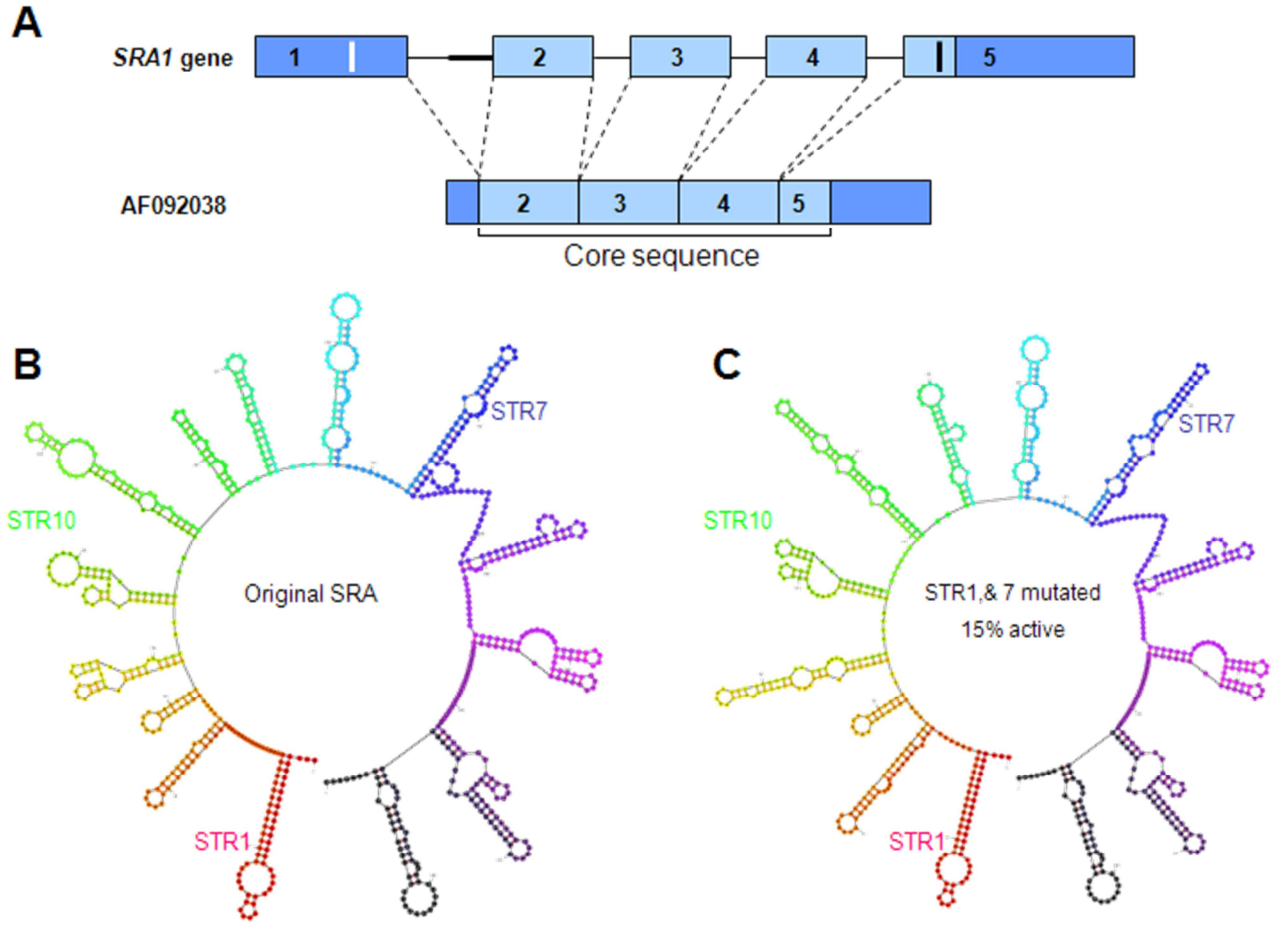

Figure 1. SRA1 genomic structure and core sequence. A) SRA sequences were originally described, differing in their 5' and 3' extremities, but sharing a central core sequence depicted in light blue (Lanz et al., 1999). One sequence has been registered with the NCBI nucleotide database (AF092038). Alignment with chromosome 5q31.3 genomic sequence is provided. Introns and exons are represented by black lines and blue boxes, respectively. **B)** Schematic profile of the predicted secondary structure of human core SRA RNA. The secondary structure profile of SRA core sequence has been modeled using Mfold software (Zuker, 2003). Detailed structure of STR1, 10, 7 (Lanz et al., 2002) is provided. **C)** By doing site-directed mutagenesis experiment, six secondary structural motifs (STR1, 9, 10, 7, 11, 12) have been identified to participate in co-activation respectively. Especially, silent mutations in both SRT1 and STR7 of SRA could nullify above 80% SRA co-activation function (Lanz et al., 2002).

Firstly, SRA's coactivation function is activated by two pseudouridylases, Pus1p and Pus3p, which have also been characterized as co-activators (Zhao et al., 2007). This modification alters the secondary structure and rigidity of the target SRA RNA molecules to promote proper folding, resulting in synergized co-activation function (Charette and Gray, 2000). The other positive regulators include the receptor co-activator 1 (SRC-1) (Lanz et al., 1999) and the RNA helicases P68/72 (Watanabe et al., 2001). SRC-1 belongs to p160 family co-activators (SRC1, SRC2/TIF2 and SRC3/AIB1), which can recruit other co-regulators to steroid receptors as well as promote a functional synergy between AF-1 and AF-2 domains (Louet and O'Malley, 2007; McKenna et al., 1999; Smith and O'Malley, 2004). Using co-immunoprecipitation from an expression system consisting of Xenopus oocytes programmed with in vitro generated RNA, SRA was found to associate with SRC-1 (Lanz et al., 1999). The p72/p68 proteins are DEAD-box RNA binding helicases that can physically interact with p160 family proteins and with ERα. AF-1 region (Caretti et al., 2007). The p72/p68 is able to bind to SRA through a well conserved motif in the DEAD box and synergizes with SRA and SRC2/TIF2 to co-activate ERα activity in the presence of estradiol (Caretti et al., 2006).

On the other side, SRA may also serve as a platform to recruit some negative regulators consisting of the SMRT/HDAC1 associated repressor protein (SHARP) (Shi et al., 2001) and the SRA stem-loop interacting RNA binding protein (SLIRP) (Hatchell et al., 2006). SHARP was found to physically interact with corepressors through its repression domain (RD) whereas it interacts with SRA through a RNA recognition motif (RRM) (Shi et al., 2001). Similarly, SLIRP specifically binds to SRA STR-7 and attenuates SRA-mediated transactivation of endogenous ER (Hatchell et al., 2006).

The emerging model of SRA action on ERα signaling had been summarized: Pus1p pseudouridylates specific SRA RNA uridine residues, leading to an optimum configuration of this RNA.

The resulting active form of SRA, could stabilize complexes with p68 and SRC-1. In this case, transcription of target genes with suitable ERE will occur. In contrast, interaction with the negative regulators SLIRP and SHARP with SRA RNA may result in the inhibition of ER-mediated transcription. It has been proposed that they might act by sequestrating SRA by destabilizing the complex SRA/SRC-1 or by recruiting the nuclear receptor corepressor N-CoR at the promoter region of silenced genes (Leygue, 2007).

2.5 A broader biological role played by SRA

It has been previously established that SRA action is not exclusively limited to increasing steroid receptor activity. Indeed it was also confirmed that SRA enhance the activity of other nuclear receptor (NRs), such as retinoic acid receptors, thyroid receptors (Zhao et al., 2004; Xu and Koenig, 2004) as well as the activity of MyoD, a transcription factor involved in skeletal myogenesis (Caretti et al., 2006; Caretti et al., 2007); SF-1 and DAX-1, orphan NRs that plays critical roles in the regulation of sex determination, adrenal development steroidogenesis (Xu et al., 2009). Recently, Foulds et al. investigated the global changes in gene expression by microarray analyses in two human cancer cell lines when SRA RNA was depleted by small interfering RNAs (Foulds et al., 2010). Unexpectedly, only a small subset of direct estrogen receptor-target genes was affected in estradiol-treated MCF-7 cells. However, they found many target genes involved in diverse biological roles such as glucose uptake, cellular signaling, T3 hormone generation were altered upon SRA depletion. This suggests SRA has a much broader upstream biological impact within the cell than simply a corgualtor of ER-signaling.

2.6 SRA RNA expression and relevance to breast cancer

Different SRA transcripts, detected by Northern blot, have been observed in normal human tissues (Lanz et al., 1999). SRA seems highly expressed in liver, skeletal muscle, adrenal gland and the pituitary gland, whereas intermediate expression levels are seen in the placenta, lung, kidney and pancreas. Interestingly, brain and other typical steroid-responsive tissues such as prostate, breast, uterus and ovary contained low levels of SRA RNA (Lanz et al., 1999). However, SRA RNA expression, assessed by RT-PCR amplification, is increased during breast and ovarian tumorigenesis (Lanz et al., 2003; Leygue et al., 1999; Hussein-Fikret and Fuller, 2005). Interestingly, SRA over-expression might characterize particular subtypes of lesions among different tumors. Indeed, serous ovarian tumors expressed higher levels of SRA than granulosa cell tumors (Hussein-Fikret and Fuller, 2005).

The involvement of SRA in ER action suggests possible SRA role in breast tumor pathology. Indeed, ER-α-positive/PR-negative breast tumors expressed more SRA than ER-α-positive/PR-positive breast tumors (Leygue et al., 1999), whereas Tamoxifen-sensitive and resistant breast tumors express similar levels (Murphy et al., 2002). However, generation of transgenic mice has however demonstrated that over-expression of the core SRA sequence in the mammary gland only led to pre-neoplastic lesions but was not sufficient per se to induce tumorigenesis (Lanz et al., 2003). Notably, SRA gene depleted MDA-MB-231 cells are less invasive than control cells, indicating this gene might be also critical for invasion (Foulds et al., 2010).

3. Coding SRA and SRAP

3.1 Discovery of SRAP

Kawashima et al. reported in 2003 the cloning of a new rat SRA cDNA mostly identical to the core SRA sequence from exon 2 to exon 5. This cDNA was,

however translatable *in vitro* encoding a putative 16 kD protein starting at the third methionine codon of the rat SRA cDNA sequence (Kawashima et al., 2003). It should be stressed that the existence of a corresponding endogenous 16 kD SRAP has never been proved.

In the nucleotide database of the National Center for Biotechnology Information (NCBI), most human SRA sequences contain an intact core sequence (exon-2 to exon-5) but differ in their 5'-extremity. Interestingly, some variants having 5' end extention contain two start codons with a large open reading frame potentially encoding a 236/237 amino acid peptide. These cDNAs, as opposed to the original SRA, were translatable *in vitro*, as well as *in vivo*, leading to the production of a protein localized both in the cytoplasm and the nucleus (Emberley et al., 2003). In addition, sequence of SRAP is highly conserved among chordate and the presence of endogenous SRAP had been found in the testes, uterus, ovary and prostate, as well as mammary gland, lung and heart (Chooniedass-Kothari et al., 2004). Altogether, accumulated data has demonstrated that SRA1 gene products consist of two characteristic entities: a functional RNA, which through its core sequence, can co-activate transcription factor and a protein whose function remains yet to be fully understood.

3.2 Function of SRAP

Chooniedass-Kothari et al. reported the existence of putative endogenous human SRA protein in breast cancer cells (Chooniedass-Kothari et al., 2006). A decreased response to ERα activity was observed in MCF-7 cells stably transfected with SRAP suggested that this protein might repress estrogen receptor activities (Chooniedass-Kothari et al., 2006). This result contrasts with Kawashima's results, who found that the transient transfection of full length rat SRA coding sequence and led to an activation of the response to androgen (Kurisu et al., 2006). It should be pointed out that, both coding sequence of SRA used by these two groups also contains the functional core sequence of SRA RNA proven to co-activate ERα. Therefore, it is difficult to draw any conclusions regarding the individual function of SRAP on estrogen receptor activities when functional SRA RNA and SRAP protein are co-expressed.

In order to understand the functional role of SRAP independently of SRA RNA, two different groups have investigated physical protein properties by tandem mass spectrometric analysis of SRAP co-immunoprecipitation samples (Jung et al., 2005; Chooniedass-Kothari et al., 2010). Interestingly, both groups showed that SRAP is able to interact with transcriptional regulators. In Chooniedass-Kothari's unpublished results using mass spectrometry, MBD3 (methyl-CpG binding domain protein 3, a member of the nucleosome remodeling and histone deacetylase complex, Nurd), BAF 57 (a core subunit of SWI/SNF chromatin remodeling complex) and YB-1 (Y-box bindng protein, a general transcription factor) have been found to interact with SRAP (Jung et al., 2005; Chooniedass-Kothari et al., 2010). By using a similar approach, Jung et al. also found that the transcription regulators, such as, BAF 170 (BRG1 associated factor 170, also belonging to SWI/SNF chromatin remodeling complex) and YB-1 are associated with SRAP (Jung et al., 2005). It is necessary to point out that different cell line models and antibodies were used in these two groups. Jung et al. used Hela cell lines and 743 antibody (commercial available rabbit polyclonal antibody) whereas Chooniedass-Kothari used MCF7 cells stably over-expressed V5 tagged SRAP and V5 antibody.

Interestingly, nobody has confirmed any protein-protein interaction between SRAP and those potential partners by co-immunoprecipitation experiments.

The observation that SRAP forms complexes with transcription factors by mass spectrometric analysis led us to investigate its direct association with transcription factors.

By using recombinant SRAP and protein arrays, Chooniedass-Kothari found that SRAP interact with different transcription factors including ERα and ERβ with different binding affinities (Chooniedass-Kothari et al., 2010). To further validate the interaction between ER and SRAP, we performed GST pull down assay and a direct interaction between GST-SRAP and both full length radio-labeled estrogen receptor α and β was observed (Chooniedass-Kothari et al., 2010). Interestingly, Kawashima showed that SRAP is also able to directly interact with the AF-2 domain of AR *in vitro* by doing GST pull down assay (Kawashima et al., 2003).

3.3 Alternative RNA splicing of SRA gene in breast cancer

The balance between co-activators and co-repressors may ultimately controls estrogen action in a given tissue (Lonard and O'Malley, 2006). A direct participation of this balance during breast tumorigenesis and cancer progression is now suspected, and a search for possible means to control it has started worldwide (Perissi and Rosenfeld, 2005; Hall and McDonnell, 2005). Alternative splicing of SRA gene might control the balance between the coding and non-coding SRA, and ultimately might function as the potential mechanism to regulate the balance between co-activators and co-repressors.

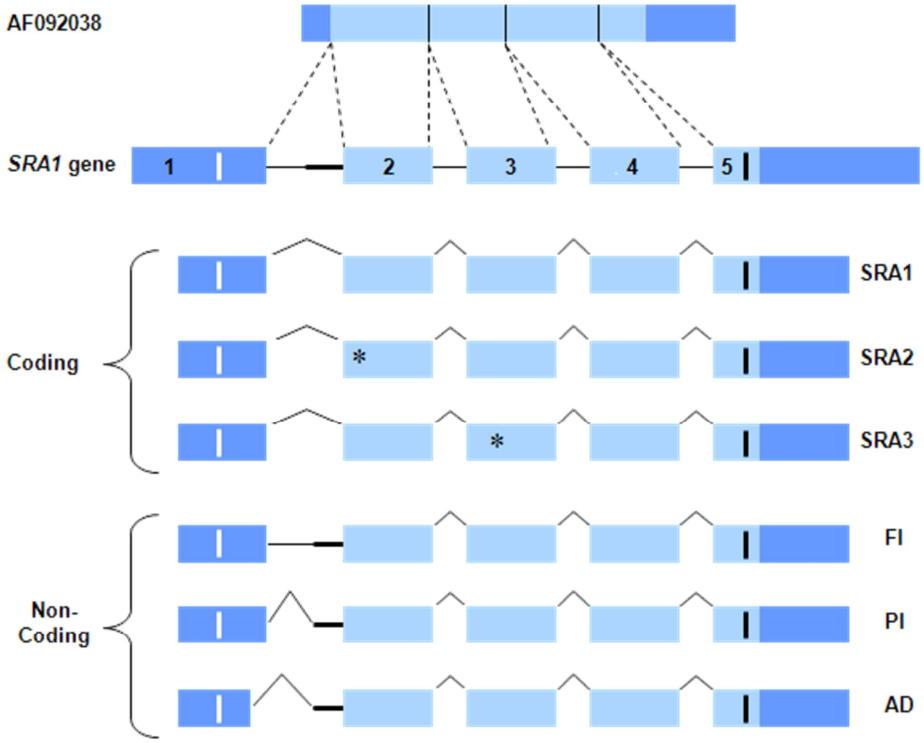

Figure 2: Coding and non-coding SRA transcripts in human breast cancer cells. SRA1 gene, located on chromosome 5q31.3, consists of 5 exons (boxes) and 4 introns (plain lines). The originally described SRA sequence (AF092038) contains a core sequence (light blue), necessary and sufficient for SRA RNAs to act as co-activators (Lanz et al., 1999). Three coding isoforms have now been identified (SRA1, SRA2, SRA3), which mainly differ from AF092038 by an extended 5'-extremity containing AUG initiating codons (vertical white bar in exon 1). The stop codon of the resulting open reading frame is depicted by a black vertical bar in exon5. Black stars in exon 2 and 3 correspond to a point mutation (position 98 of the core: U to C) and a point mutation followed by a full codon (position 271 of the core: G to CGAC), respectively. Three non-coding SRA isoforms containing a differentially-spliced intron-1 have been characterized: FI, full intron-1 retention; PI, partial intron-1 retention; AD, alternative 5' donor and partial intron retention. Thick straight line, 60 bp of intron 1 retained in PI; triangulated lines represent splicing events (Modified from Cooper et al. 2009).

Both non-coding and coding SRA transcripts co-exist in breast cells (Figure 2, Hube et al., 2006). Using a previously validated triple-primer PCR (TP-PCR) assay (Leygue et al., 1996), which allows co-amplification and relative quantification of two transcripts sharing a common region but differing in another, we found that breast cancer cell lines co-expressed normally spliced coding SRA RNA as well as SRA RNA containing intron-1 (Hube et al., 2006). Interestingly, breast cancer cell lines differ in their relative levels of coding/non-coding SRA transcripts. In particular, the three most invasive cell lines (MDA-MB-231, 468, and BT-20) expressed the highest, whereas the "closest to normal" MCF-10A1 breast cells expressed the lowest relative levels of SRA intron-1 RNA. This suggests that a balance changed toward the production of non-coding SRA1 RNA in breast cells might be associated with growth and/or invasion properties (Hube et al., 2006).

Alternative splicing events result from the relative local concentration of RNA binding proteins within the microenvironnement surrounding the nascent pre-mRNA (Mercatante et al., 2001). We were recently able to artificially alter the balance between coding and non-coding SRA1 RNAs in T5 breast cancer cells using a previously described splicing-switching oligonucleotide strategy (Mercatante et al., 2001; Mercatante and Kole, 2002). This approach resulted in an increase in the production of intron retained transcripts, decrease in the expression of SRAP, resulting in an observed significant increase in the expression of the urokinase plasminogen activator (uPA, PLAU), gene intimately linked to invasion mechanisms (Harbeck et al., 2004) as well as of ERβ, involved, as highlighted earlier, in breast cancer cell growth (Han et al., 2005).

3.4 SRAP expression and relevance to breast cancer

SRAP expression was assessed by Tissue Microarray (TMA) analysis of 372 breast tumors (Yan et al., 2009). SRAP levels were significantly higher in estrogen receptor-alpha positive, in progesterone receptor positive and in older patients (age > 64). When considering ER+ tumors, PR+ tumors, or young patients (≤ 64 years), patients with high SRAP expression had a significantly worse breast cancer specific survival (BCSS) than patients with low SRAP levels. SRAP also appeared as a very powerful indicator of poor prognostic for BCSS in the subset of ER+, node negative and young breast cancer patients. Altogether suggest that SRAP levels might provide additional information on potential risk of recurrence and negative outcome in a specific set of patients.

4. Conclusion

Accumulated data suggest that the bi-faceted SRA/SRAP system, including SRA non-coding RNA and SRA protein, regulates estrogen receptor signaling pathways and plays a critical role in breast tumorigenesis and tumor progression. SRA is the first example of a new kind of molecules active at both RNA as well as at the protein levels. Investigating and understanding this bi-faceted system might open a new era of novel preventive or therapeutic strategies for breast cancer patients.

Acknowledgements

This work is supported by the Canadian Institute of Health Research / the Canadian Breast Cancer Research Alliance (MOP-129794) and the CancerCare Manitoba Foundation (761017028). Y Yan has been supported by the MHRC (Manitoba Health Research Council) Studentship.

Abbreviations

AF-1: activation function 1
AF-2: activation function 2
AR: androgen receptor
DAX-1: dosage-sensitive sex reversal-adrenal hypoplasia congenital critical region on X chromosome gene 1; NR0B1
DBD: DNA binding domain
ER: estrogen receptor
ERE: estrogen receptor
GR: glucocorticoid receptor
LBD: ligand binding domain
MBD3: methyl-CpG binding domain protein 3
NRs: nuclear receptors
NCoR: nuclear co-repressor
PLAU: urokinase plasminogen activator
PR: progesterone receptor
Pus1p: pseudouridine synthase 1
Pus3p: pseudouridine syntheses 3
SERM: selective estrogen receptor modulators
SF-1: nuclear receptor steroidogenic factor 1
SDM: site-directed mutatagenesis
SHARP: SMRT/HDAC1 associated repressor protein
SLIRP: SRA stem-loop interacting RNA binding protein
SRA: steroid receptor RNA activator
SRAP: steroid receptor RNA activator protein
SR: serine/arginine-rich proteins
SRC-1: steroid receptor co-activator 1
STR: secondary structural motif
YB-1: Y-box bindng protein

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This article should be referenced as such:

Yan Y, Cooper C, Leygue E. The roles of SRA1 gene in breast cancer. Atlas Genet Cytogenet Oncol Haematol. 2010; 14(12):1186-1192.