

Original citation:

Grammatopoulos, Dimitris K.. (2014) R : CRH-R splicing in estrogen-sensitive breast cancer. Cell Cycle, Volume 13 (Number 5). pp. 687-688.

Permanent WRAP url:

<http://wrap.warwick.ac.uk/67600>

Copyright and reuse:

The Warwick Research Archive Portal (WRAP) makes this work of researchers of the University of Warwick available open access under the following conditions.

This article is made available under the Creative Commons Attribution-NonCommercial 3.0 Unported (CC BY-NC 3.0) license and may be reused according to the conditions of the license. For more details see: <http://creativecommons.org/licenses/by-nc/3.0/>

A note on versions:

The version presented in WRAP is the published version, or, version of record, and may be cited as it appears here.

For more information, please contact the WRAP Team at: publications@warwick.ac.uk

warwick**publications**wrap

highlight your research

<http://wrap.warwick.ac.uk>

This article was downloaded by: [137.205.202.194]

On: 26 May 2015, At: 03:53

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Cell Cycle

Publication details, including instructions for authors and subscription information:
<http://www.tandfonline.com/loi/kccy20>

CRH-R splicing in estrogen-sensitive breast cancer

Dimitris K Grammatopoulos^a

^a Division of Metabolic and Vascular Health; Warwick Medical School; University of Warwick; Coventry, UK

Published online: 21 Jan 2014.



[Click for updates](#)

To cite this article: Dimitris K Grammatopoulos (2014) CRH-R splicing in estrogen-sensitive breast cancer, *Cell Cycle*, 13:5, 687-688, DOI: [10.4161/cc.27858](https://doi.org/10.4161/cc.27858)

To link to this article: <http://dx.doi.org/10.4161/cc.27858>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Versions of published Taylor & Francis and Routledge Open articles and Taylor & Francis and Routledge Open Select articles posted to institutional or subject repositories or any other third-party website are without warranty from Taylor & Francis of any kind, either expressed or implied, including, but not limited to, warranties of merchantability, fitness for a particular purpose, or non-infringement. Any opinions and views expressed in this article are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor & Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

It is essential that you check the license status of any given Open and Open Select article to confirm conditions of access and use.

CRH-R splicing in estrogen-sensitive breast cancer

Dimitris K Grammatopoulos

Division of Metabolic and Vascular Health; Warwick Medical School; University of Warwick; Coventry, UK

Alternative pre-mRNA splicing contributes in the acquired genomic alterations involved in the pathobiology of cancer development and progression.¹ In normal biological systems, this mechanism allows protein complexity and diversity by increasing gene coding capacity and promoting expression of several related proteins with diverse and even antagonistic functions. However, in pathological settings such as cancer, mutations in splicing regulatory elements and/or alterations in the cellular splicing machinery can change splicing patterns and result in the generation of aberrantly spliced pre-mRNAs that favor development of the malignant state.

In breast cancer, an overall upregulation of splicing factors and remarkable changes in the splicing mechanisms has been identified, characterized by exon skip and intron retention as the predominant events.² These result in cancer-specific splice variants for various genes with important roles in regulation of tumor cell proliferation, DNA damage, adhesion, invasion, angiogenesis and apoptosis, and response to therapy. For example, a survivin variant with pro-apoptotic properties that acts as a naturally occurring antagonist of the anti-apoptotic oncogene BIRC5 is downregulated in breast carcinoma. Increased expression of alternatively spliced cadherin-11 variants enhances breast cancer cell invasive potential. Also, MDM2, a phosphoprotein that participates in the proteasomal degradation of the tumor suppressor p53, can generate more than 40 aberrant alternatively spliced transcripts. Expression of specific MDM2 variant transcripts has been correlated with a shorter overall survival of breast cancer patients. VEGF isoforms have been shown to be prognostic

for survival in patients with node-positive breast cancer, whereas CD44 novel variant isoforms are overexpressed and preferentially located in metastatic breast cancer tissues.

Modifications in the alternative splicing profile of CD44 during mammary gland tumorigenesis, are associated with dramatic changes in abundance of the arginine-serine-rich (SR) family of splicing factors,³ known to influence alternative splicing decisions in a wide variety of genes. Our recent study⁴ revealed that one of these SR nuclear proteins, SRp55, encoded by the *SRSF6* gene, is targeted and downregulated by estrogens in an estrogen-sensitive malignant mammary epithelial cell line. This strengthens emerging evidence that points toward an important role of estrogens as regulators of alternative splicing through modulation of SR factors expression: a recent study⁵ in ER-positive breast cancer cells, identified altered splicing events in 154 genes under the influence of estrogens, with 40% of genes lacking intragenic ER α binding sites. The list of targets included genes important for cell apoptosis, and this event is linked to resistance to apoptosis and response to therapy. This study also suggested that the *SRSF7* factor is estrogen-inducible and may contribute to estrogen-regulated alternative splicing of genes without ER α binding sites by causing splicing as a secondary event. SRp55 has been previously implicated in the pathogenic mechanisms of breast cancer, and depletion of SRp55 levels is associated with increased resistance to DNA damage, whereas mutations in the *SRSF6* gene have been identified in breast and colorectal cancer; such mutations could transform these factors as oncoproteins or tumor suppressors, depending on

their antagonistic functions on splice site selection.

SRp55 has been previously shown to control the splicing profile of several tumor-associated genes, such as *FGFR1*, *CD44*, and *KIT*; our study identified the type 1 corticotropin-releasing hormone receptor (CRH-R1), a member of the class B1 G-protein-coupled receptors (GPCR) as a novel target. In mammals, CRH-R1 mediates and controls cellular actions of CRH, the hormonal master switch of adaptive responses to stress. Estrogen-induced changes in SRp55 levels appear to alter splicing direction of the *CRHR1* gene toward exon-12 skipping and increase expression of signaling-impaired, “exon-12-less” CRH-R1 mRNA variants, thus limiting cellular responsiveness to CRH actions. This in-frame deletion of 42 bp from the CRH-R1 mRNA transcript leads to loss of 14 amino acids from the C-terminal end of TMD7.

Potentially, this is a splicing “hot spot” conserved throughout evolution, since the 42-bp exon is present in the genomic sequence of all members of the B1 GPCRs and several members of the ancestral family of adhesion GPCRs,⁶ suggesting a function preserved across different members.

These findings have expanded our appreciation of the complexity of CRH signaling regulation. The biological consequences of E2-driven neutralization of CRH signaling through aberrant splicing in breast cancer cells are intriguing and might be of relevance for a wider group of GPCRs and their cognate agonists in cancer or other pathophysiological settings such as pregnancy and labor.⁷ Exposure to chronic stress represents a major risk factor for the development and progression of cancer, and CRH-induced molecular

Correspondence to: Dimitris K Grammatopoulos; Email: d.grammatopoulos@warwick.ac.uk

Submitted: 10/09/2013; Accepted: 10/28/2013; Published Online: 01/21/2014

<http://dx.doi.org/10.4161/cc.27858>

Comment on: Lal S, et al. *Sci Signal* 2013; 6:ra53; PMID:23821771; <http://dx.doi.org/10.1126/scisignal.2003926>

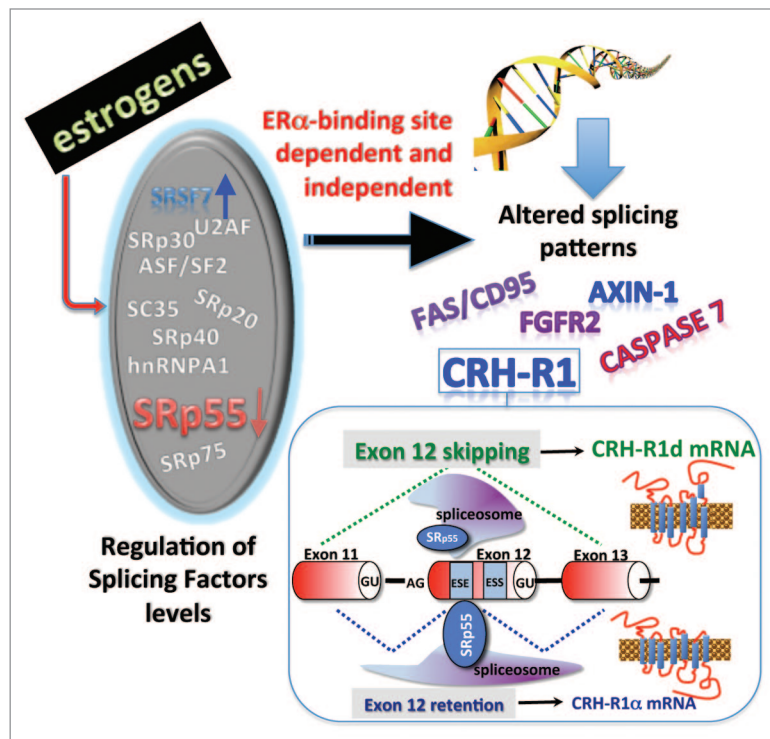


Figure 1. Estrogen-induced splicing in breast cancer cells and consequences for cell responsiveness to CRH. Estrogens are able to induce a plethora of splicing events in breast cancer cells, via regulation of expression of a distinct subset of splicing factors. This allows generation of cancer-specific splice variants for various genes with important roles in tumor cell biology. Downregulation of SRp55 alters splicing direction of the *CRHR1* gene toward exon-12 skipping and increases expression of “exon-12-less” CRH-R1 mRNA variants. These variants exhibit impaired signaling, and, therefore, this molecular event might act as a signaling checkpoint by limiting cellular responsiveness to CRH actions.

mechanisms activated in response to stressful stimuli might increase disease susceptibility and facilitate neoplastic

transformation and cancer pathogenesis.⁸ Although at present we can only speculate about the actions of CRH in breast cancer

cells, it appears that CRH exerts complex tumor-promoting as well as anti-tumor roles in ER-positive breast cancer cells, through activation of an intricate network of kinase-triggered signaling pathways and regulation of multiple transcriptional targets.

This emerging pattern of CRH actions thus highlights the need of further studies to elucidate this, in particular in the context of estrogen-sensitive breast cancer. Nevertheless, this novel functional link between estrogens and aberrant *CRHR1* splicing pattern provides new insights about cellular checkpoints of responses to hormonal signal transduction. (Fig. 1)

References

1. Pajares MJ, et al. *Lancet Oncol* 2007; 8:349-57; PMID:17395108; [http://dx.doi.org/10.1016/S1470-2045\(07\)70104-3](http://dx.doi.org/10.1016/S1470-2045(07)70104-3)
2. Eswaran J, et al. *Sci Rep* 2013; 3:1689; PMID:23604310; <http://dx.doi.org/10.1038/srep01689>
3. Stickeler E, et al. *Oncogene* 1999; 18:3574-82; PMID:10380879; <http://dx.doi.org/10.1038/sj.onc.1202671>
4. Lal S, et al. *Sci Signal* 2013; 6:ra53; PMID:23821771; <http://dx.doi.org/10.1126/scisignal.2003926>
5. Bhat-Nakshatri P, et al. *BMC Med Genomics* 2013; 6:21; PMID:23758675; <http://dx.doi.org/10.1186/1755-8794-6-21>
6. Markovic D, et al. *Trends Biochem Sci* 2009; 34:443-52; PMID:19733082; <http://dx.doi.org/10.1016/j.tibs.2009.06.002>
7. Markovic D, et al. *Endocrinology* 2007; 148:3205-13; PMID:17431005; <http://dx.doi.org/10.1210/en.2007-0095>
8. Licinio J, et al. *Lancet* 1995; 346:104-6; PMID:7626147; [http://dx.doi.org/10.1016/S0140-6736\(95\)92119-2](http://dx.doi.org/10.1016/S0140-6736(95)92119-2)