Commentary

Emerging roles in prolactin-mediated BRCA1 function

Da Li[1], Qi-Jun Wu[2]

[1]Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, Shenyang 110004, China; [2]Department of Clinical Epidemiology, Shengjing Hospital of China Medical University, Shenyang 110004, China

Correspondence to: Qi-Jun Wu. Department of Clinical Epidemiology, Shengjing Hospital of China Medical University, Shenyang 110004, China. Email: wuqijun111@sina.com; leeda@ymail.com.

Comment on: Chen KH, Walker AM. Prolactin inhibits a major tumor-suppressive function of wild type BRCA1. Cancer Lett 2016;375:293-302.

Submitted Apr 13, 2016. Accepted for publication Apr 21, 2016.
doi: 10.21037/tcr.2016.06.01
View this article at: http://dx.doi.org/10.21037/tcr.2016.06.01

In a recent issue of *Cancer Letters*, Chen *et al*. reported that prolactin may inhibit a major tumor-suppressive function of BRCA1 by interfering with the BRCA1-related cell cycle inhibitor, p21 (1). These findings are interesting and will open up a controversial discussion on the role of prolactin in tumorigenesis.

Two decades ago, interest was sparked by the discovery of the breast cancer susceptibility gene BRCA1, and germline mutations of BRCA1 confer an increased lifetime risk of 56–80% for breast cancer (2). Prolactin is essential for normal breast development and lactation. Accumulating evidence indicates that (I) prolactin may promote the formation of breast cancer in rodents and elevated serum prolactin is related to increased risk of estrogen-receptor positive breast cancer in women (3); (II) prolactin can stimulate the proliferation, migration, and survival of breast cancer cells by the cell-surface prolactin receptor (4); (III) hyperprolactinemia, defined by prolactin levels of more than 530 mIU/L in women, has been implicated for a long time in the etiology and prognosis of breast cancer (5). Notably, emerging evidence has suggested possible links between BRCA1 and prolactin. For example, (I) BRCA1 is upregulated (6,7) and Stat5a forms a complex with BRCA1 (8) in response to prolactin stimulation in human breast cancer cells, and along with the maximal enhancement of cell proliferation (6), suppresses apoptosis (7); (II) prolactin may block the nuclear translocation of the vitamin D receptor through the interaction with BRCA1 in osteosarcoma cells (9); (III) the differentiation of terminal end buds was impaired in BRCA1 mutant mice with preservation of prolactin-mediated alveolar differentiation (10); (IV) BRCA1 levels increase during early pregnancy and decrease during late pregnancy and lactation when prolactin levels are high (11). Of even greater note, Chen *et al*. found that prolactin may inhibit BRCA1 function through p21 (1). However, several lines of evidence indicate that an NAD-dependent protein, deacetylase sirtuin 1 (SIRT1), may play an important part in prolactin-mediated BRCA1 and/or p21 function: (I) our data suggested that prolactin led to a substantial decrease in NAD levels that inhibited NAD-related SIRT1 activity in ovarian granulosa cells, although they may not regulate the SIRT1 levels (*Figure 1*); (II) prolactin contains an NADH binding site (12), and NAD is a potent activator and substrate of SIRT1 (13); (III) SIRT1 overactivation-mediated NAD consumption may inhibit BRCA1 function (13); (IV) SIRT1 was a potential regulator of p21 (14). Therefore, the emerging picture from these studies prompted us to evaluate a possible link among prolactin, NAD, SIRT1, BRCA1 and p21. Taken together, we suggested that what the authors observed in their study may be a reflection of changes in prolactin-mediated SIRT1 activity. Overall, this may improve our understanding of the basic molecular mechanism underlying prolactin-related tumorigenesis.

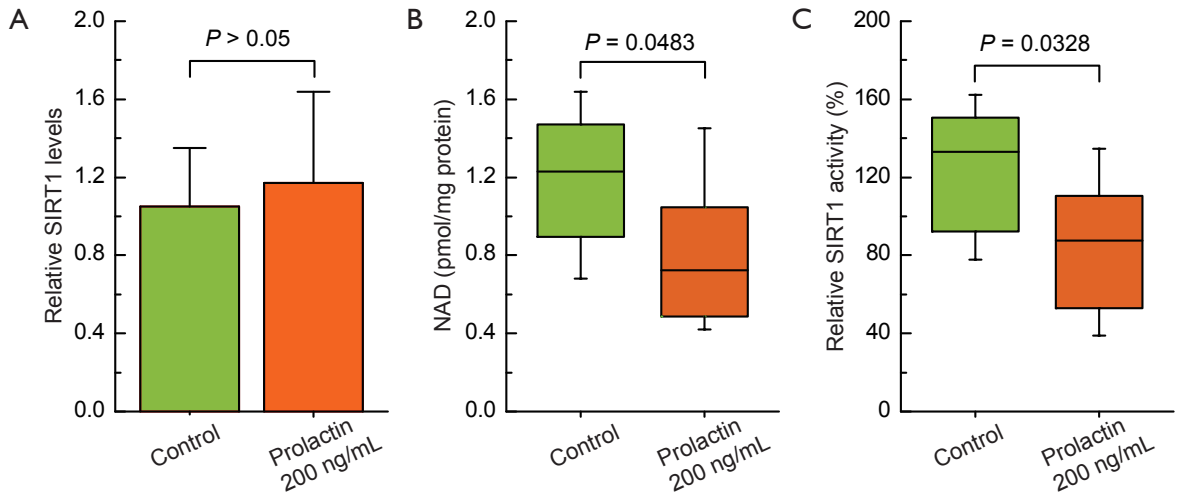

Figure 1 Intracellular SIRT1 levels and NAD-dependent SIRT1 activity after treatment with and without prolactin. (A-C) SIRT1 levels, NAD levels and SIRT1 activity were measured after treatment with and without prolactin, bar graphs show mean ± SD (n=8 for each group).

Acknowledgments

Funding: This work was supported by the Fok Ying Tung Education Foundation (No.151039), Natural Science Foundation of China (No. 81402130), and the Doctoral Start-up Foundation of Liaoning Province (No. 20141045 and 201501007).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, Translational Cancer Research. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.06.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Chen KH, Walker AM. Prolactin inhibits a major tumor-suppressive function of wild type BRCA1. Cancer Lett 2016;375:293-302.
2. Millot GA, Carvalho MA, Caputo SM, et al. A guide for functional analysis of BRCA1 variants of uncertain significance. Hum Mutat 2012;33:1526-37.
3. Sato T, Tran TH, Peck AR, et al. Global profiling of prolactin-modulated transcripts in breast cancer in vivo. Mol Cancer 2013;12:59.
4. Galsgaard ED, Rasmussen BB, Folkesson CG, et al. Re-evaluation of the prolactin receptor expression in human breast cancer. J Endocrinol 2009;201:115-28.
5. Froes Brandao D, Strasser-Weippl K, Goss PE. Prolactin and breast cancer: The need to avoid undertreatment of serious psychiatric illnesses in breast cancer patients: a review. Cancer 2016;122:184-8.
6. Favy DA, Rio P, Maurizis JC, et al. Prolactin-dependent up-regulation of BRCA1 expression in human breast cancer cell lines. Biochem Biophys Res Commun 1999;258:284-91.
7. Harvey PW. Human relevance of rodent prolactin-induced non-genotoxic mammary carcinogenesis: prolactin

involvement in human breast cancer and significance for toxicology risk assessments. J Appl Toxicol 2005;25:179-83.
8. Vidarsson H, Mikaelsdottir EK, Rafnar T, et al. BRCA1 and BRCA2 bind Stat5a and suppress its transcriptional activity. FEBS Lett 2002;532:247-52.
9. Deng C, Ueda E, Chen KE, et al. Prolactin blocks nuclear translocation of VDR by regulating its interaction with BRCA1 in osteosarcoma cells. Mol Endocrinol 2009;23:226-36.
10. Jones LP, Tilli MT, Assefnia S, et al. Activation of estrogen signaling pathways collaborates with loss of Brca1 to promote development of ERalpha-negative and ERalpha-positive mammary preneoplasia and cancer. Oncogene 2008;27:794-802.
11. Hietala M, Olsson H, Jernström H. Prolactin levels, breast-feeding and milk production in a cohort of young healthy women from high-risk breast cancer families: implications for breast cancer risk. Fam Cancer 2008;7:221-8.
12. Trad CH, Chavan AJ, Clemens J, et al. Identification and characterization of a nucleotide binding site of ovine prolactin with 2-azido-NAD. Arch Biochem Biophys 1993;304:58-64.
13. Li D, Bi FF, Chen NN, et al. A novel crosstalk between BRCA1 and sirtuin 1 in ovarian cancer. Sci Rep 2014;4:6666.
14. Atkins KM, Thomas LL, Barroso-González J, et al. The multifunctional sorting protein PACS-2 regulates SIRT1-mediated deacetylation of p53 to modulate p21-dependent cell-cycle arrest. Cell Rep 2014;8:1545-57.

Cite this article as: Li D, Wu QJ. Emerging roles in prolactin-mediated BRCA1 function. Transl Cancer Res 2016;5(S1):S136-S138. doi: 10.21037/tcr.2016.06.01

