



Emerging roles of prolactin-mediated BRCA1 function

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We appreciate the commentary on our article Chen *et al.* "Prolactin inhibits a major tumor-suppressive function of wild type BRCA1" (1) by Li and Wu (2), most particularly because it indicates a growing interest in the tumorigenic properties of prolactin, whose role in a variety of cancers remains understudied.

By way of background, the question our study (1) posed was, given the importance of BRCA1 as a tumor suppressor in the breast and ovaries and the fact that ~90% of tumors have normal BRCA1, how is the tumor-suppressive function of normal BRCA1 on the cell cycle overcome in the vast majority of cancers?

BRCA1 is tumor-suppressive in a number of ways, including DNA damage repair, transcriptional regulation, and ubiquitination (3). Among the transcriptional functions is upregulation of the cell cycle inhibitor, p21, and this was the focus of the study in question (1). Contrary to what one might expect, prolactin, growth hormone and interleukin-2 all increase expression of BRCA1 (1) while also promoting both physiological and pathological cell proliferation (4). A common feature of these ligands is activation of Stat5. Our article (1) showed that when Stat5 was phosphorylated it formed a physical complex with BRCA1. This, in turn, prevented the BRCA1 from transactivating the p21 promoter. In other words, the phosphorylation of Stat5 allowed for both elevated BRCA1 and increased cell proliferation, a design feature that would allow other BRCA1 functions such as DNA repair to proceed under circumstances of physiologically-appropriate cell proliferation. However, the mechanism also pertains to circumstances of pathological proliferation, and explains how cells can escape cell cycle control by normal BRCA1.

In the commentary by Li and Wu (2), the suggestion is made that prolactin regulation of Sirt1 activity may mediate our results. However, our findings directly demonstrated the formation of a physical complex between phosphorylated Stat5 and BRCA1 and, unlike non-complexed BRCA1,

this complex was unable to transactivate the p21 promoter. Transactivation was restored by a dominant negative Stat5 in the continued presence of a Stat5-activating ligand. That is not to say that prolactin does not also regulate Sirt1 activity, as Li and Wu demonstrated (2), and through this mechanism may also affect p21 regulation of the cell cycle. Indeed, from our own work we know that prolactin regulates the amount and availability of functional p21 in the cell by a number of additional mechanisms, including destabilization of p21 mRNA by targeted miRNA and destabilization of p21 protein through post-translational modification (unpublished data). The mechanism proposed by Li and Wu (2) adds another potential pathway to the regulation of p21 and/or BRCA1 by prolactin. P21 is crucial to appropriate regulation of the cell cycle; one would therefore expect there to be multiple interacting mechanisms regulating the amount, location and activity.

Using ovarian granulosa cells, Li and Wu (2) show that prolactin lowers NAD levels and, since Sirt1 activity is dependent on NAD (5), Sirt1 activity goes down as a result. Sirt1 is a general protein deacetylase (5) with wide-ranging effects. These include deacetylation of histones and therefore multiple effects on cancer-related gene expression. In addition, Sirt1 deacetylates and therefore inactivates p53 (5). If Sirt1 activity goes down with prolactin treatment, this would raise activity of p53 and should result in increased expression of p21 (6), i.e., less proliferation in response to prolactin and this is not seen. However, this pathway may not be relevant in cancers with mutant p53 and would not be relevant to what we described since we used mostly p53-inactive cell lines (1). Effects caused by changes in histone acetylation would be manifold and any outcome very difficult to predict.

In regard to prolactin-BRCA1-Sirt1 interactions, it is also hard to predict the outcome. For example, our work and the work of others referenced therein (1) shows that prolactin increases expression of BRCA1. BRCA1 binds to the promoter of SIRT1 and increases Sirt1 expression

in breast cancer (7), a finding confirmed by Li *et al.* in ovarian cancer (8). One would therefore expect prolactin to increase levels of Sirt1, but Li and Wu did not find this (2). However, this lack of effect of prolactin on Sirt1 levels is consistent with RNAseq data from our laboratory showing that knockdown of the Stat5-activating form of the prolactin receptor does not significantly alter SIRT1 expression (unpublished data), and with SIRT1 not being among the genes identified as prolactin-responsive by Sato *et al.* (9). One explanation for a lack of effect on expression of SIRT1 could be the presence of a feedback mechanism that limits cellular levels. In this regard, Eades *et al.* have shown that miR-200a targets SIRT1 (10). In the cancer literature, Sirt1 has been shown to have both pro- and anti-carcinogenic effects, dependent on circumstance and tissue. For example, reduced Sirt1 prevents EMT-like transformation driven by TGF- β in normal mammary epithelial cells, suggesting that higher Sirt1 amounts/activity would promote tumorigenesis (10). By contrast, Sirt1 inhibits NF- κ B, which is major mediator of inflammation, tumor cell survival, and cancer metastasis, i.e., in this instance, Sirt1 would be anti-carcinogenic (11). Just as we had to work out how there could be an increased amount, but decreased activity of BRCA1 in regard to its influence on p21 levels, it will be important to work out the molecular interactions regulating Sirt1 amounts versus activity and the eventual effect on carcinogenesis.

In summary, we do not dispute the possibility that there is a prolactin-Sirt1-mediated effect on p21, but do maintain that its existence would not negate our very directly demonstrated findings in regard to the prolactin-phosphorylated Stat5-BRCA1 complex and the effect on p21 expression.

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appropriately investigated and resolved.

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