Emerging roles in prolactin-mediated BRCA1 function

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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 Stat5α 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.

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Footnote

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