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Menopausal estrogen deprivation activates steroid sensitive stem cells (3SC) and local estrogen biosynthesis: A model for breast cancer development

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Abstract We propose a hypothesis for breast cancer (BC) development and its implications for BC prevention. We describe a model in which some breast cells function as both stem cells and steroid sensors (steroid sensitive stem cells). Estrogen receptors on those cells could be upregulated in women who had increased cumulative exposure to estrogen, leading to their progressive sensitization. At menopause, such women experience considerable decline of estrogen concentration in their blood. Consequently, the sensitized stem cells activate mechanisms of local estrogen synthesis including the activation of aromatase. The intracrine build-up of estrogen and its metabolites induces proliferation and genetic dysfunction. Eventually, a normal stem cell transforms into an estrogen-sensitive cancer stem cell that is capable of tumor initiation and delineation into other phenotypes of cancer cells. This hypothesis is supported by significant in-vitro and clinical research evidence. According to this model, we suggest that estrogen therapy could be protective against BC. Alternatively, aromatase inhibitors are expected to be effective in BC prevention. A combination of AIs and estrogen might augment the preventative merits of both drugs and maintain a good tolerability profile for long-term prevention protocols.

Introduction

Estrogen has a primary role in breast cancer (BC) pathophysiology by inducing mitogenesis, genotoxicity, epigenetic and occasionally mutational changes [1,2]. In menopausal women's breast, estrogen acts as a key

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intracrine–paracrine molecule [3–5]. The intra-tumoral estrogen concentrations in breast cancer may reach up to 20 times the corresponding blood levels [6]. Aromatase is the enzyme catalyzing the last step of estrogen biosynthesis from androgens and appears to be the most crucial in determining the overall estrogen concentration inside the breast. Indeed, over-expression of aromatase in the mammary glands of transgenic mice was associated with increased incidence of hyperplasia, dysphasia, fibroadenomas and nuclear abnormalities; all are considered to be pre-cancerous lesions [7]. There is an evident association between the expression of aromatase and the menopausal status of a woman. For instance the aromatase gene (*CYP19*) was expressed in the breast tissue of normal menopausal women significantly more than in young menstruating women [8]. Similarly, the aromatase activity and aromatase gene expression were significantly higher in menopausal BC patients compared to premenopausal patients [9,10]. Meanwhile, growing data supports the presence of normal breast stem cells with potential for malignant transformation into cancer stem cells that are capable of further driving of tumor growth and metastasis; generally referred to as the ''cancer stem cell theory'' [11].

Hypothesis

We hypothesize that steroid sensitive stem cells (3SC) exist in the normal breast comprising a side population of cells rich in stem cell properties and steroid receptors (including estrogen receptors). The estrogen receptors on these stem cells are upregulated by a positive feedback mechanism especially in women who are exposed to high cumulative estrogen throughout their reproductive life (from both endogenous and exogenous sources). Around menopause, those women become hypersensitive to the considerable circulatory estrogen deprivation. The sensitized stem cells and their abundant estrogen receptors signal feedback stimulation for local estrogen synthesis, in a trial to restore the high premenopausal estrogenic milieu they used. This is mainly achieved by the activation of breast aromatase and other relevant enzymes. The subsequent local build-up of estrogen, a potent mitogenic factor, induces the multiplication of the 3SC. Simultaneously, the hydroxy metabolites of estrogen induce DNA damage, by adduct formation and other epigenetic and mutational effects, to help establish a cancer stem cell (CSC) that is capable of tumor initiation and progression (Fig. 1). Interruption of this cascade by either preventing the acute estrogenic withdrawal effect on already sensitized receptors (using estrogen therapy) or by blocking the synthesis of estrogen (using aromatase inhibitors therapy) could be a successful strategy for BC prevention in high-risk women.

Evaluation of the hypothesis

Evidence from in-vitro and in-vivo studies

Characterization of normal and malignant breast stem cells

There is substantial evidence that cancer is generated by a tumor-initiating cell that has properties similar to those of other stem cells [12–14]. Breast cancer-initiating cells with several stem cell properties have also been identified [15,16].

Finding normal breast stem cells positive for steroid receptors

It is well known that most breast cancers express steroidal hormone receptors (~75%) [17,18]. A series of recent important studies by Clarke et al. have demonstrated a correlation between stem cell properties and the expression of steroid receptors (ER-alpha and PR) amongst normal human breast cells. They proposed a model of a side population of stem cells that act as ''steroid sensors'' and could be the cancer-initiating cells [13,19,20].

Estrogen as a negative feedback regulator of its own biosynthesis

Estradiol was shown, in several studies, to significantly inhibit the activity of both aromatase and sulfatase (the enzyme catalyzing the production of active estrogens form estrogen sulphates) in breast cancer cell lines. A negative feedback of estrogen on its own production has been, therefore, suggested [21–23]. Also, breast cancer cells which were deprived of estrogen long-term have expressed significantly higher aromatase activity compared to cells that were not estrogen deprived. The enzyme was inhibited upon re-exposure of the cells to estrogen [24]. In baboons, bilateral ovariectomy increased the breast aromatase activity while treatment with exogenous estrogens resulted in significant reduction of the aromatase mRNA and the activity of the enzyme. Based on these results, increased aromatase activity in menopausal women was suggested to maintain high local estrogen concentrations inside the breast [25].

Evidence from clinical studies

Aromatase activity was slightly elevated in breast cancer patients who were not using estrogenic hormone replacement therapy (HRT) compared to HRT users [24]. Also, when estradiol was added to cancerous and normal tissues obtained from breast cancer patients, it expressed strong anti-sulfatase activity [23].

According to the initial report of the Women Health Initiative (WHI) study, women who received estrogen-alone replacement therapy (CEE arm) for an average follow up period of 7.1 years had an overall non-significant decrease of BC incidence compared to women who were given placebo ($P < 0.06$) [26]. In a sub-analysis of these results, it was found that estrogen therapy indeed caused a significant reduction of BC incidence in sub-groups of women including women who were first time users during the trial, women who were adherent to the treatment and those who had no family history of BC and no past history of benign breast disease [27].

Discussion and implications

Based on this hypothesis, we propose that a low dose estrogen therapy could be of potential benefit for BC prevention particularly when given to menopausal women