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Function of the vitamin D endocrine system in mammary gland and breast cancer

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ABSTRACT

The nuclear receptor for 1α,25-dihydroxycholecalciferol (1,25D), the active form of vitamin D, has anti-tumor actions in many tissues. The vitamin D receptor (VDR) is expressed in normal mammary gland and in many human breast cancers suggesting it may represent an important tumor suppressor gene in this tissue. When activated by 1,25D, VDR modulates multiple cellular pathways including those related to energy metabolism, terminal differentiation and inflammation. There is compelling pre-clinical evidence that alterations in vitamin D status affect breast cancer development and progression, while clinical and epidemiological data are suggestive but not entirely consistent. The demonstration that breast cells express CYP27B1 (which converts the precursor vitamin D metabolite 25D to the active metabolite 1,25D) and CYP24A1 (which degrades both 25D and 1,25D) provides insight into the difficulties inherent in using dietary vitamin D, sun exposure and/or serum biomarkers of vitamin D status to predict disease outcomes. Emerging evidence suggests that the normally tight balance between CYP27B1 and CYP24A1 becomes deregulated during cancer development, leading to abrogation of the tumor suppressive effects triggered by VDR. Research aimed at understanding the mechanisms that govern uptake, storage, metabolism and actions of vitamin D steroids in normal and neoplastic breast tissue remain an urgent priority.

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1. Introduction to vitamin D and breast cancer

Breast cancer is a heterogeneous disease with multiple subtypes, each of which have distinct cells of origin and etiology (Skibinski and Kuperwasser, 2015). As such, there is no single identified cause of breast cancer, and treatment strategies are increasingly directed towards the underlying molecular defects unique to each subtype. The vast majority of breast cancers arise from epithelial cells in either the ducts or lobules that have sustained genetic and epigenetic alterations leading to aberrant growth control and disruption of intracellular signaling at the tissue level. Physiological and pathological influences such as hormonal milieu, obesity, diet, age, and inflammation contribute to

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disease progression through multiple mechanisms. Although survival rates are increasing for breast cancer overall, certain subtypes, such as triple negative breast cancer (TNBC) and inflammatory breast cancer (IBC), are especially aggressive and associated with drug resistance leading to poor survival. Overall, breast cancer is associated with a 20% mortality rate within the first 5 years after diagnosis. The high prevalence of breast cancer (over 250,000 cases diagnosed annually in the US) warrants continued research into more effective treatment options and prevention strategies.

Nuclear receptors, such as those activated by the steroid hormones estrogen and progesterone, are critical regulators of mammary gland development and have complex roles in breast cancer etiology. As such, these receptors represent important targets for both prevention and treatment of breast cancer. The vitamin D receptor (VDR), another member of the nuclear receptor family which is highly expressed in breast tissue, is activated by its hormonal ligand 1,25-dihydroxyvitamin D (1,25D). As described in more detail below, activation of VDR by 1,25D modulates the phenotype of normal mammary cells and breast cancer cells in culture. Dietary and pharmacologic studies in animal models of breast cancer have also provided compelling evidence for tumor suppressive actions of VDR agonists (Narvaez et al., 2014; Feldman et al., 2014). Deletion of the VDR gene in mice enhances the development of hyperplasias and hormone independent mammary tumors in response to chemical carcinogens and sensitizes the mammary gland to tumorigenesis driven by various oncogenes. Collectively these laboratory data suggest that the VDR acts as a tumor suppressor in mammary gland. If so, then it is logical to assume that human breast cancer risk or progression would be related to vitamin D status (typically measured as serum 25-hydroxyvitamin D [25D]). Furthermore, such an association might explain, at least in part, the geography and seasonality of breast cancer, differences in disease incidence between Caucasian and African American populations and the impact of obesity, as all of these factors are known to modulate vitamin D status (Yao and Ambrosone, 2013; Kim et al., 2014; Bilinski and Boyages, 2013; Morton and Thompson, 2013; Shirazi et al., 2013). More importantly, confirmation of a link between vitamin D status and breast cancer would raise the possibility that breast cancer development or survival could be modified by strategies to increase serum 25D such as food fortification, use of dietary supplements or prudent increases in sun exposure. While a substantial amount of epidemiological and clinical data support such associations, the cumulative data is inconsistent (Yao and Ambrosone, 2013; Eliassen et al., 2016; Jacobs et al., 2016; Cadeau et al., 2016; Shekarriz-Foumani and Khodaie, 2016). In many epidemiological studies, the impact of vitamin D status appeared to be limited to sub-groups in a cohort with specific attributes, such as pre- or post-menopausal status, presence of obesity, specific tumor subtype, race/ethnicity or genetic polymorphisms. With respect to polymorphisms, considerable effort has been directed at defining genetic determinants of serum 25D that underlie response to supplementation and how these may affect chronic disease incidence and progression. For breast cancer, extensive analyses have yielded conflicting data as recently reviewed (Jolliffe et al., 2016).

Only a few vitamin D supplementation trials with breast cancer as a dedicated end-point have been conducted, and these have suffered from major limitations (underpowered, not specific for vitamin D, inappropriate dose, etc) as discussed by Lappe and Heaney (2012). Despite these limitations, some analyses of the data from these trials support a benefit of vitamin D supplementation on breast cancer incidence or severity (Cauley et al., 2013; Neuhouser et al., 2012; Bolland et al., 2011), although often this benefit is explained or modified by other lifestyle factors (ie, physical activity, BMI or hormone replacement therapy).

This review will focus on recent cellular and molecular studies that have demonstrated the importance of autocrine/paracrine vitamin D metabolism in breast cancer and identified novel aspects of VDR signaling in breast cancer. Areas in which additional research efforts are needed will be highlighted.

2. VDR expression and function in normal and neoplastic breast tissue

Although it has long been recognized that the VDR is expressed in normal mammary tissue and in breast cancers, detailed insight into its distribution, regulation and function are still emerging. With the public availability of large genomic datasets such as The Cancer Genome Atlas (TGCA), it is now possible to evaluate the frequency of genomic *VDR* changes (mutations, amplifications, deletions and mRNA expression profiles) in large cohorts of human cancers (Cancer Genome Atlas N, 2012). Examination of the TGCA METABRIC dataset (which contains over 2500 samples), indicates that only 4% of invasive human breast tumors exhibit alterations in *VDR* sequence or expression (Fig. 1). In the few cases where VDR alterations were observed, the most frequent change was an unexpected up-regulation of VDR mRNA. While the significance of this finding is unclear, the TGCA data indicates that the majority of breast cancers do not exhibit loss of function mutations or reduced expression of the VDR gene.

Changes in VDR protein expression during development and tumorigenesis have also been extensively studied. In mouse mammary gland, VDR protein is expressed in all major cell types (basal and luminal epithelial cells, cap cells, stromal cells) but its expression is not temporally or spatially uniform (Zinser et al., 2002; Zinser and Welsh, 2004a). VDR is developmentally regulated with induction during pubertal growth and peak expression during pregnancy and lactation. In the epithelial compartment of the murine gland, the strongest VDR staining is found in the differentiated luminal cells suggesting that VDR expression is inversely associated with proliferation. Similarly, high content multiplex immunofluorescent analysis of normal human breast epithelium (Santagata et al., 2014) indicated that VDR positive cells are enriched in the differentiated luminal cell layer and do not co-localize with proliferating (Ki67 positive) cells. This study also examined co-localization of VDR, estrogen receptor (ER) and androgen receptor (AR) in a panel of breast cancers and correlated receptor expression with patient outcomes. VDR expression was detected in >90% of cells of ER+ and HER2+ tumors but at markedly lower frequency in TNBCs. Examination of over 3000 human

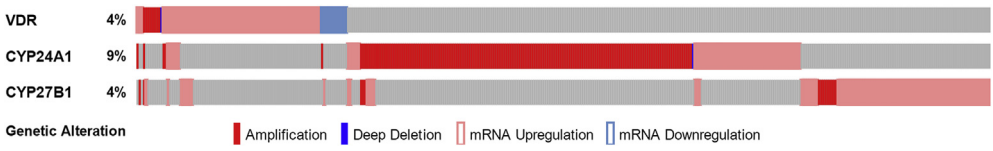

Fig. 1. *Analysis of genomic alterations in VDR, CYP24A1 and CYP27B1 in human breast tumors.* This oncoprint reports cases in which the indicated alterations (amplification, deep deletion, mRNA upregulation or mRNA downregulation) in VDR, CYP24A1 or CYP27B1 were detected in individual tumor samples. The TGCA dataset utilized was the Breast Cancer (METABRIC) consisting of 2509 patients. Data analysis was conducted within the cBIOPortal for Cancer Genomics at http://www.cbioportal.org/.