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Calcium, Ca^{2+}-Sensing Receptor and Breast Cancer

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1. Introduction

Breast cancer is the most commonly diagnosed cancer and one of the leading causes of cancer-associated death among women worldwide. Each year, more than one million new cases of breast cancer are diagnosed worldwide, and an estimated 370,000 women die from breast cancer (1, 2). Ca^{2+} as an important nutrient from dairy products functions as an important signalling messenger from the beginning to the end of our life, and plays a critical role in many physiological processes such as gene transcription, cell growth, proliferation, migration, differentiation and apoptosis (3-11). Many of these processes are associated with tumorigenesis and cancer progression. Dysregulation of calcium homeostasis and signaling causes many human diseases, including mammary gland pathophysiology and breast cancer (3, 4, 5 and 9).

2. Ca^{2+} and breast cancer

Ca^{2+} is a ubiquitous cellular signal which has been strongly implicated in triggering and regulating various cell functions by Ca^{2+}-regulated proteins and their signaling pathways (3-11). The concentration of free extracellular Ca^{2+} (Ca_o^{2+}) in our serum is kept constant by processing that constantly feeds Ca^{2+} into, and withdraws it from the extracellular fluid, such as dietary calcium intake and bone calcium turnover (5-7). Decreases in the concentration of free Ca_o^{2+} in plasma (hypocalcemia) result in increased neuromuscular irritability and tetany. Increases in total serum Ca_o^{2+} (hypercalcemia) can result in fatigue, depression, mental confusion, anorexia, nausea, vomiting, constipation, reversible renal tubular defects, increased urination, alteration in the electrocardiogram (a short QT interval), and cardiac arrhythmias as well as renal insufficiency and calcification in the kidney, skin, vessels, lungs, heart and stomach. There is a ~12,000-fold Ca^{2+}-gradient between intracellular (~100 nM) and extracellular (~1.2 mM) free Ca^{2+} concentrations in cells. To maintain this Ca^{2+} gradient, cells chelate, compartmentalize, or remove Ca^{2+} from the cytoplasm (3). Regulation of cellular processes via Ca^{2+}-signaling such as binding of Ca^{2+} to proteins, change of intracellular Ca^{2+} (Ca_i^{2+}) concentrations, and modification of other

protein functions by Ca^{2+} have been shown to play important roles in cancer initiation, tumor formation, tumor progression, metastasis, invasion and angiogenesis (12-14). For instance, Ca^{2+} can activate transcription factors such as nuclear factor of activated T cells (NFAT) resulting in modulation of cellular transcription (11), regulate cell proliferation promoting cancer cell progression (4, 9, 12), and modulate poly-(ADP-ribose) polymerase-1 (PARP1), mitochondrial membrane permeabilization and DNA damage leading to apoptosis and necrosis (10, 13). By mobilizing the release of Ca_i^{2+} from endoplasmic reticulum, angiogenic factors such as vascular endothelial growth factor can increase Ca_i^{2+} that in turn promote angiogenesis (14), Ca^{2+} signaling also plays an important role in cellular motility such as during tumor invasion and metastasis (4, 5, 9, 12).

2.1 Ca^{2+} intake and breast cancer risk

Calcium is a threshold nutrient and is the most abundant mineral element in the body. Dietary calcium has an important impact on bone metabolism and bone health, and is also among a number of nutritional factors suggested to be associated with cancer. Higher intakes of Ca^{2+} are reported to increase the risk of prostate cancer (15, 16) and lung cancer (17), and to reduce the risk of ovarian cancer and colorectal cancers (18, 19). Many epidemiological studies around the world that evaluated the association between Ca^{2+} intake and the risk of breast cancer have been published (20-32). Table I summaries thirteen studies from eight countries during the last five years. Most of these epidemiological studies indicate no significant association between Ca^{2+} intake and the risk of breast cancer, and some of these investigations show a negative association (20-32). Epidemiologic studies suggest that higher intake of Ca^{2+} may not be associated with breast tumorigenesis.

Studies	Calcium	Breast cancer risk	References
Chinese women	Food	No association/reduction	20, 21
Norwegian women	Dairy product	No significant association	22
Canadian women	Food and supplements	No association	23
German women	Food	No association	24
Swedish women	Food	No association	25
American women	Food and supplements	No association/modest reduction	26-30
Japanese women	Food and supplements	Reduction	31
French women	Food	Negative association	32

Table 1. Calcium intake and breast cancer risk.

2.2 Serum Ca^{2+} and breast cancer risk

As one of many nutrients in dairy products, it is difficult to study the role of calcium intake in breast cancer risk. Serum calcium is maintained within a fairly narrow range from 8.5 to 10 .5 mg/dl (2 .2 to 2 .7 mmol/L). Given the emerging interest in the potential role of Ca^{2+} in the etiology of breast cancer, several investigations focus on analyzing the relationship between the levels of serum calcium and the risk of breast cancer. In 2007, the first cohort study of 7847 women performed by Almquist et al. (33) evaluated serum calcium in relation to breast cancer risk. They found a positive association between total calcium and breast cancer risk among overweight postmenopausal women. In follow-up studies in which 462 women were diagnosed with incident breast cancer, they found that serum calcium levels in premenopausal and overweight women were positively associated with increased tumor

aggressiveness as determined by a higher risk of nodal metastasis (34, 35). Recently, these results were supported by Martin et al. who also found that serum calcium levels among postmenopausal women are positively associated with incident breast cancer in white women (36), while another study found no association between total serum calcium and breast cancer risk among postmenopausal women (37). Although more studies on the relationship between serum calcium and breast cancer risk are necessary, hypercalcemia defined as an abnormal elevation in serum calcium levels is a frequent complication of breast cancer (38-41). This suggests the Ca_o^{2+} could play an important role in the regulation of breast cancer progression.

2.3 Bone metastasis of breast cancer cells and Ca^{2+} release

Hypercalcemia, which has been found in 30-40% of breast cancer patients, is the most frequent metabolic complication of breast cancer (38-41). In a significant minority of patients, cancer-induced hypercalcemia is caused by systemic secretion of parathyroid hormone-related protein (PTHrP) by cancer cells, and PTHrP causes increased bone resorption and enhances renal retention of calcium (42, 43). Most commonly, hypercalcemia occurs in patients with multiple bone metastases. Breast cancer cell metastases to bone often cause bone destruction or osteolysis, and leads to the release of growth factors from the bone matrix (e.g., transforming growth factor, insulin-like growth factor, basic fibroblast growth factor), and the release of large quantities of Ca^{2+} into the bone microenvironment (44-49). The growth factors can stimulate breast cancer cell proliferation (47), while Ca^{2+} also plays an important role in crosstalk between tumor cells and bone microenvironment to promote a vicious cycle of tumor cell growth and bone destruction.

3. Ca^{2+}-sensing receptor and breast cancer

Recent studies have demonstrated that some G protein coupled receptors (GPCR) such as endothelin receptors, chemokine receptors and lysophosphatidic acid receptors play an important role in tumorigenesis and metastasis of multiple human cancers (50-52). Some other GPCRs, for instance neuropeptide receptors, adenosine A_{2B} receptor, P_{2Y} receptor, bradykinin receptor, thrombin receptor, metabotropic glutamate receptors, estrogen receptor, and EGF-like module containing mucin-like hormone receptor 2 are also expressed at a significantly higher level in cancer tissues and have been implicated in cancer progression (53-57). The Ca^{2+}-sensing receptor (CaR) has a characteristic seven transmembrane domain GPCR structure and was initially characterized as a sensor for modulating parathyroid hormone and calcitonin release in response to change in blood Ca^{2+} levels (58). The metastasis of breast cancer cells to bone result in osteolysis and lead to the release of large quantities of Ca^{2+} into the bone microenvironment (45, 46). This Ca_o^{2+} can be a primary signaling molecule and act through the CaR that directly regulates multiple signaling pathways involved in breast cancer cell growth, proliferation, differentiation, apoptosis and migration (58, 59), and through the Ca^{2+} channels which elevate intracellular Ca^{2+} (Ca_i^{2+}) levels to modulate Ca^{2+}-dependent proteins (60).

3.1 CaR expression and breast cancer

3.1.1 Up-regulation of CaR expression in breast cancer cells and specimens

The CaR is expressed in the epithelial ducts of the normal human breast, and the level of expression is associated with mammary gland development, with lower levels in pregnancy

and involution, low levels before pregnancy and higher levels with lactation (61). These physiological changes in CaR expression are involved in the control of PTHrP secretion that feeds back to regulate Ca^{2+} influxes to the mammary glands. These influxes regulate the proliferation of normal mammary epithelial cells. During lactation, bone loss is rapid and completely reversible upon weaning, and large amounts of calcium are transferred into milk, placing nursing mothers under calcemic stress. Bone turnover increases and bone mass decreases, presumably to free skeletal calcium for milk production (62, 63). It is known that the receptor is also expressed in breast carcinomas and breast cancer cell lines (64). Using an anti-CaR antibody with peptide blocking to demonstrate specificity, we (65) recently reported that the levels of CaR expression are significantly increased in breast cancer cell lines compared to nonmalignant breast cell lines (Fig. 1). Mihai et al. analyzed the relationship between the levels of CaR expression and bone metastases in 108 breast cancer patients, and found that patients with higher CaR expression are more likely to develop bone metastases (66). The higher Ca_o^{2+} concentration in the erosion sites of breast cancer metastasis and up-regulation of CaR expression in breast cancer cells could lead to cell signaling abnormalities. This suggests the potential changes in CaR-mediated signaling in breast cancer cells.

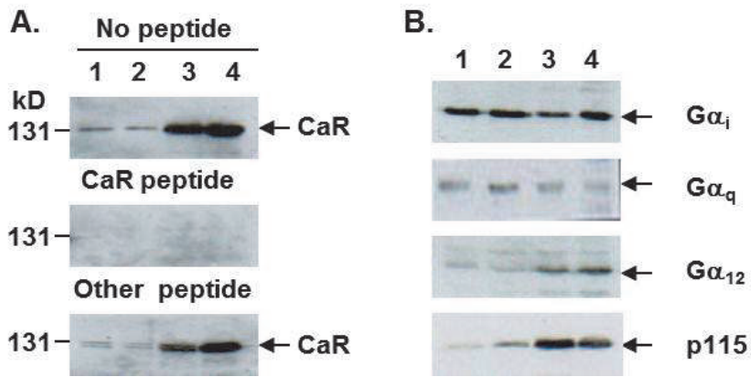

Fig. 1. **Expression of CaR, G protein and p115RhoGEF in normal breast cells and breast cancer cells.** Equal amounts of protein from Hs 578Bst (lane 1), MCF-10A (lane 2), MDA-MB-231 (lane 3) and MCF-7 cell (lane 4) lysates were processed for immunoblotting using antibodies against different proteins as shown on the right. A) Peptide blocking: anti-CaR antibody incubated with no peptide (top) immunogenic peptide (middle) or non-specific peptide (bottom); B) $G\alpha_i$ (top), $G\alpha_q$ (upper middle) $G\alpha_{12}$ (lower middle) and p115RhoGEF (p115, bottom).

3.1.2 Alteration of other CaR-signaling components in breast cancer

Like other GPCRs, the CaR signaling cascade contains four major components: receptor, G protein (heterotrimeric $\alpha\beta\gamma$), regulators of G-protein signaling (RGS) protein, and effectors (67). Current evidence shows that the CaR couples to G_s, G_i, G_q, and $G_{12/13}$ and can be regulated by RGS4 and p115-RhoGEF (58, 65, 68, and 69). Kelly et al. (70) recently reported that expression of $G\alpha_{12}$ is significantly up-regulated in the earliest stages of breast cancer by immunohistochemical detection, and that the inhibition of $G\alpha_{12}$ signaling reduces the metastatic dissemination of breast cancer cells in an animal model. $G\alpha_{12/13}$ acts through p115RhoGEF, a RGS protein with GAP activity for the $G\alpha_{12/13}$ subunits and guanine

nucleotide exchange activity for the small G protein Rho (67). To explore the role of CaR-mediated signaling in breast cancer cells, we compared the levels of G protein ($G\alpha_i$, $G\alpha_q$ and $G\alpha_{12}$) and p115RhoGEF expression in two nonmalignant breast cell lines (Hs 578Bst and MCF-10A) and two breast cancer cell lines (MDA-MB-231, estrogen receptor/progesterone receptor negative and highly invasive, and MCF-7, estrogen receptor/progesterone receptor positive and weakly invasive), and found that the levels of $G\alpha_{12}$ and p115RhoGEF expression are dramatically up-regulated in two breast cancer cell lines (Fig. 1). Up-regulation of CaR, $G\alpha_{12}$ and p115RhoGEF expression in breast cancer cells indicates a potential signaling role in breast tumorigenesis and cancer progression.

3.2 CaR signaling in breast cancer cells

3.2.1 CaR signaling regulates the activation of choline kinase in breast cancer cells

Alteration in choline phospholipid metabolism as detected by nuclear magnetic resonance is a common feature of breast and many other cancer cells or tumors (71-76). Evidence from animal and cell studies as well as preclinical and clinical studies shows significant increases in phosphocholine (P-cho) levels in a range of human tumors (breast, colon, prostate, lung, neuroblastoma and lymphomas, etc) (77-82). Choline kinase (ChoK), the enzyme expressed in various tissues and that catalyzes the phosphorylation of choline to P-cho, is the first phosphorylation reaction in the CDP-choline pathway for the biosysthesis of phosphatidylcholine (83). Based on increased ChoK expression and activity in cancer cells and tumors, and increased ChoK activity in *ras* transformed cells (77-82, 84), ChoK has been proposed to play a role in the onset or progression of human cancer (breast, colon, prostate and lung, etc) and to be a target for developing anti-tumor drugs and an avenue for pharmaceutical therapy. Earlier studies also showed that various growth factors such as epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, insulin-dependent growth factor and vascular endothelial growth factor enhance ChoK activity during tumor formation (85-87).

Because overexpression of the CaR-signaling components (Fig. 1 and refs 65, 66, 70) and increases of ChoK activity and P-cho production (72, 77-82) have consistently been observed in breast cancer cells and breast tumors, and metastasis of breast cancer cells to bone leads to the release of large quantities of Ca^{2+} (45, 46), it is possible that up-regulation of CaR signaling leads to a significantly altered choline phospholipid metabolism which regulates breast cancer cell proliferation. To evaluate the roles of Ca^{2+}- and CaR-regulated ChoK in breast cancer cells, we (65) recently prelabeled Hs 578Bst cells, MCF-10A cells, MDA-MB-231 cells and MCF-7 cells with [^{3}H]choline to study Ca^{2+}-induced ChoK activation and P-cho production, and found that Ca^{2+}-induced [^{3}H]P-cho production was significantly increased in breast cancer cells compared to the nonmalignant breast cells in time- or dose-dependent manners. Using an anti-CaR antibody to block Ca_o^{2+} binding to the CaR and siRNA to silence CaR gene expression, we further demonstrated that [^{3}H]P-cho production in response to Ca_o^{2+}-stimulation was CaR-dependent. By analyzing cellular lipid profiles and using siRNA to silence ChoK expression, we defined that the production of [^{3}H]P-cho was primarily related to CaR-induced ChoK activation. Treatment of the cells with either pertussis toxin or C_3 exoenzyme, and co-immunoprecipiation of $G\alpha_{12}$ with the CaR, we found that the enhancement of ChoK activation and P-cho production in breast cancer cells occurs via a CaR-$G\alpha_{12}$-Rho signaling pathway.

3.2.2 CaR signaling regulates breast cancer cell proliferation

Because the CaR stimulates ChoK activation in breast cancer cells, understanding ChoK activation and P-cho production in the regulation of cell proliferation is very important. Glunde et al. (81) recently knocked down ChoK expression by transfecting ChoK-specific siRNA and short hairpin RNA into breast cancer cells and found that down-regulation of ChoK expression reduced cell proliferation measured by proliferating cell nuclear antigen and Ki-67, and induced cell differentiation measured by cytosolic lipid droplet formation and expression of galectin-3. Shah et al. (82) showed that overexpression of ChoK in human breast cancer cells increases invasiveness and drug resistance. Overexpression of ChoK in HEK 293 cells leads to up-regulation of cyclin D1 and cyclin D3 expression and down-regulation of TGFβ receptor1, cyclin G2, cyclin-dependent kinase inhibitor 1A (p21, Cip1) and 1B (p27, Kip1) expression, which is involved in the regulation of TGFβ signaling (88). These data suggest that up- or down-regulation of ChoK expression and activity is associated with cell proliferation. Furthermore, the increase of cellular P-cho observed in cancer cells and tissues (71-79) indicates that P-cho produced by ChoK activation may play an important role in the regulation of cell function. Earlier studies in cell models showed direct evidence that treatment of fibroblasts with P-cho increases DNA synthesis and the effect is enhanced with other agonists such as ATP and insulin (89). Up-regulation of ChoK activation and P-cho production in human breast cancer cells and tumors indicates that CaR-ChoK signaling plays an important role in promoting breast cancer cell proliferation.

P-cho could stimulate breast cancer cell proliferation. Many recent studies show that several synthetic alkylphosphocholines (edelfosine, miltefosine and perifosine), P-cho analogs, have been developed as a new class of anti-cancer agents. These P-cho analogs act on cellular membranes rather than the DNA, and disturb signal transduction including the inhibition of phosphatidylcholine synthesis, the inhibition of the MAP-kinase/ERK proliferative and phosphatidylinositol 3-kinase/ Akt survival pathways, the stimulation of the Stress-activated protein kinase/JNK cell death pathway, and the inhibition of cell attachment, spreading, and migration (90-94). P-cho analogs as a class of anti-tumor drugs have been used more and more in clinical studies, but exploring the molecular mechanism of how they interact with cancer cells continues.

The CaR, through the $G\alpha_{12}$-p115RhoGEF-ChoK signaling pathway, connects to the synthesis of choline-containing phospholipids and the proliferation of breast cancer cells. Recently, studies also showed that the CaR plays a role in epidermal growth factor receptor (EGFR) transactivation to regulate cell proliferation. Using H-500 rat Leydig cancer cells as a model for humoral hypercalcemia of malignancy, Tfelt-Hansen et al. showed that treatment of H-500 cells with Ca_o^{2+} stimulates PTHrP release leading to CaR-induced activation of ERK1/2 and stimulation of cellular proliferation through the transactivation of the EGFR (95, 96). El Hiani et al. further reported that high Ca_o^{2+} induced CaR activation leads to breast cancer cell proliferation, and the inhibition of EGFR kinase reduced the activation of ERK1/2, and breast cancer cell proliferation (97). This cross-talk between the CaR and the EGFR in the regulation of cell proliferation was also found in Rat-1 fibroblasts (98). All these data indicate that the CaR can act through EGFR transactivation to regulate breast cancer cell proliferation.

Bone tissue is the most common organ targeted by breast cancer cells where metastasis can directly or indirectly stimulate osteoclast-mediated bone resorption. Tumor-induced osteolysis leads to the release of large quantities of calcium. The local Ca^{2+} level at resorption sites has been reported to rise as high as 40 mM (46). Hence, metastatic breast cancer cells

could be faced with abnormally high Ca^{2+} concentrations. One recent report showed that the high Ca^{2+} concentrations through the CaR signaling pathway stimulate PTHrP expression and secretion in MCF-7 and MDA-MB-231 breast cancer cells (64). Tumor-cell derived PTHrP enhances bone remodeling and release of numerous biological factors, facilitates skeletal progression by directly stimulating tumor cell proliferation (99, 100), and promotes homotypic aggregation of breast cancer cells in suspension and three-dimensional cultures (101-103). This suggests that the Ca_o^{2+} and CaR in the bone environment can regulate a signaling network through different cell types to promote breast cancer cell proliferation.

3.2.3 CaR signaling regulates breast cancer cell migration

Elevated Ca_o^{2+} concentrations stimulate PTHrP secretion from various normal and malignant cells. PTHrP plays a central role in the development of breast cancer metastases to bone, and skeletal metastases of breast cancers express more PTHrP and maintains at the levels higher than those in normal breast epithelial cells, primary breast cancers, or nonskeletal metastases (42). By transfection of vector, mutated and wild-type PTHrP into breast cancer cells (MCF-7), the study showed that wild-type PTHrP-overexpressing cells increased cell laminin, adhesion, migration, and Matrigel invasion. Overexpression of wild-type PTHrP also increased the cell surface expression of the pro-invasive integrins α6 and β4 (104). Using Boyden Chamber and Scratch Wound migration assays, Saidak et al. (105) showed direct evidence that Ca_o^{2+} at concentrations of 2.5 mM and 5 mM induces cell migration compared to basal levels for several breast cancer cell lines. The highly bone metastatic breast cancer cells strongly respond to elevated concentrations of Ca_o^{2+} in the migration assays. Knockdown of the CaR by siRNA resulted in an inhibition of Ca_o^{2+}-induced migration, indicating the involvement of this receptor in the effect. All these data indicate that Ca_o^{2+} acts through the CaR to promote breast cancer cell migration.

Cell migration is required for cancer cells to spread, invasion and metastasis, and metastasis of cancer cells is significantly associated with increased mortality and reduced treatment effectiveness. Cell migration is achieved through dynamic remodeling of filamentous actin and of focal adhesion sites. Tu et al. (106) demonstrated the involvement of the CaR in the activation of E-cadherin signaling. Using human epidermal keratinocytes as a cell model, silencing CaR expression blocks the Ca_o^{2+}-induced formation of adherens junctions, and the association of phosphoinositide 3-kinase (PI3K) with the E-cadherin-catenin complex. Ca_o^{2+} does not stimulate tyrosine phosphorylation of β-, γ-, and p120-catenin and Fyn in the CaR-deficient keratinocytes. Further studies find that Rho GTPase is a part of the CaR-mediated signaling cascade regulating cell adhesion. Ca_o^{2+}-induced Rho activation requires a direct interaction between CaR and filamin A (107). The CaR regulated E-cadherin cell membrane localization and complex formation of E-cadherin and β-catenin was also reported in human colon carcinoma cells (108). CaR-specific siRNA and the CaR antagonist (NPS2390) can partially inhibit wound repair of human bronchial epithelial cells, and these signaling pathway(s) are associated with phospholipase C which can be blocked by U73122 and ERK1/2 which can be inhibited by PD 98059 (109). Ca_o^{2+} acts through the CaR to stimulate migration of osteoclast precursor RAW 264.7cells via the PI3K/Akt pathway but not the MAPK (ERK, p38 and JNK) pathways (110). In Boyden Chamber and Scratch Wound migration assays, Saidak et al. reported that inhibition of either ERK1/2 by U0126 or phospholipase Cβ by U73122 led to an abolition of the Ca_o^{2+}-induced migration of breast cancer cells (105). These data suggest that the CaR can regulate cell migration, however, the details of the CaR-induced breast cancer cell migration remain largely unknown.

4. Future perspective

Cloning of the CaR has provided a molecular tool to study the receptor-mediated signaling and -associated human diseases including breast cancer. Until now, most of the studies have focused on how the CaR is associated with the characteristic abnormalities in the functions of the parathyroids and kidneys, and which signaling pathways of the CaR are involved in the regulation of cell functions (Fig. 2) by CaR overexpression and RNA interference. Much remains to be learned, such as CaR expression in other tissues, including tumor tissues and the pathways that are regulated in the tissues by identifying single-nucleotide polymorphisms (SNP) in the CaR, determining whether gain or loss of function SNPs in the CaR lead to tumorigenesis and cancer progression, and by analyzing the role of CaR-mediated signaling in CaR-associated tumorigenesis and progression to develop potent and specific CaR antagonists that would be extremely useful in cancer therapy. In addition, the CaR and perhaps other sensors for calcium or other agonists for the CaR, and transactivation of other receptors such as EGF receptor by the CaR in the cells will likely regulate a wide variety of cellular functions via different signaling pathways. Therefore, understanding system biology and signalling networks controlled by CaR-signaling is important for the potential cancer therapy.

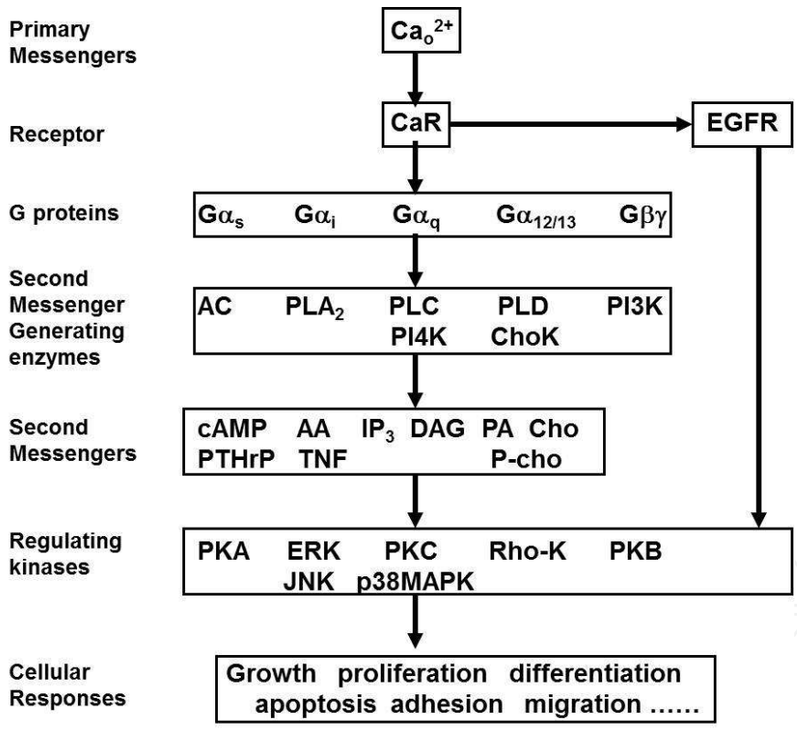

Fig. 2. **A schematic diagram of CaR-mediated signaling pathways.** Many of these signaling pathways were identified in different cell lines and heterologous expression systems, and may not all exist in breast cancer cells. CaR, Ca^{2+}-sensing receptor; EGFR, epidermal growth factor receptor; AC, adenyl cyclase; ChoK, choline kinase; PLC, phospholipase C; PLA_2, phospholipase A_2; PLD, phospholipase D; PI3K, phosphatidylinositol-3 kinase; PI4K, phosphatidylinositol-4-kinase; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; Rho-K, Rho kinases; p38MAPK, p38 mitogen-activated protein kinases; JNK, c-Jun N-terminal kinases; ERK, extracellular-signal-regulated kinases.

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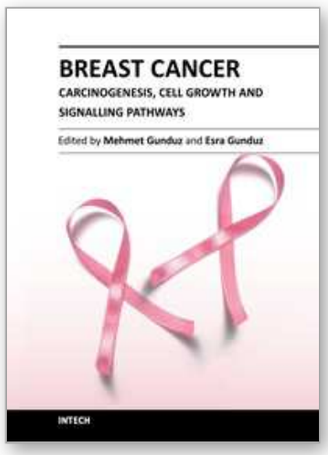

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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