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REVIEWS: CURRENT TOPICS

Bidirectional signaling of mammary epithelium and stroma: implications for breast cancer—preventive actions of dietary factors

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Abstract

The mammary gland is composed of two major cellular compartments: a highly dynamic epithelium that undergoes cycles of proliferation, differentiation and apoptosis in response to local and endocrine signals and the underlying stroma comprised of fibroblasts, endothelial cells and adipocytes, which collectively form the mammary fat pad. Breast cancer originates from subversions of normal growth regulatory pathways in mammary epithelial cells due to genetic mutations and epigenetic modifications in tumor suppressors, oncogenes and DNA repair genes. Diet is considered a highly modifiable determinant of breast cancer risk; thus, considerable efforts are focused on understanding how certain dietary factors may promote resistance of mammary epithelial cells to growth dysregulation. The recent indications that stromal cells contribute to the maintenance of the mammary epithelial 'niche' and the increasing appreciation for adipose tissue as an endocrine organ with a complex secretome have led to the novel paradigm that the mammary stromal compartment is itself a relevant target of bioactive dietary factors. In this review, we address the potential influence of dietary factors on mammary epithelial–stromal bidirectional signaling to provide mechanistic insights into how dietary factors may promote early mammary epithelial differentiation to decrease adult breast cancer risk.

Keywords: Mammary gland; Epithelium; Adipocyte; Diet; Breast cancer; Obesity

1. Introduction

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths among women in the United States. In 2009 alone, more than 190,000 new cases of invasive breast cancer were reported, which accounted for ~25% of all cancers among women in the United States [1]. Similar to all cancers, breast cancer is a genetic and epigenetic disease with diverse histopathological and clinical outcomes [2]. Although the major reasons for breast cancer deaths are complications arising from metastasis, the natural history of breast cancer involves progression through defined molecular, pathological and clinical stages [3,4]. The widely accepted view of breast tumor progression, known as linear progression [5], assumes the gradual transition of breast lesions from premalignant, hyperplastic states into ductal carcinoma *in situ*, invasive carcinoma and, finally, metastatic disease [6]. Recent clinical studies demonstrating heterogeneity in tumors from breast cancer patients now suggest that the linear progression model maybe overly simplistic [7,8]. In the more recently described diversity evolution model [9], the constant selection pressures provided by numerous environmental cues or therapeutic interventions are posited to lead to the high clonal diversity found in tumors as well as the drug resistance that may develop during treatment [10].

The mammary gland is comprised of myoepithelial and luminal epithelial cells embedded in a complex stromal matrix ('mammary fat pad') comprised predominantly of fibroblasts, adipocytes and macrophages (Fig. 1). The prevailing concept in the field is that the discrete mammary epithelial subtypes and neighboring stromal cells arise, respectively, from the asymmetric division of epithelial and mesenchymal cells of origin ('stem cells') and the subsequent differentiation of lineage-committed progenitor cells [11,12]. Emerging data on mammary stem cells have raised the possibility that this epithelial subpopulation 'sitting at the top' of the mammary epithelial hierarchy serves as initial target of oncogenic agents [11].

The transformation of normal mammary epithelial cells to malignancy is manifested as aberrant growth and survival responses to extracellular signals. The latter include those derived from the endocrine milieu, as well as from the stroma, whose physical proximity to epithelial cells allows for dynamic paracrine regulation and the integration of signals from circulating hormones and growth factors [13,14]. In a recent review, Arendt et al. [15] detailed the

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complex local and systemic contributions of the stromal compartment to normal mammary development and to malignant breast development. Molecular and phenotypic changes within the stroma affect their interactions with neighboring cells, resulting in a microenvironment that can be supportive of epithelial progression to malignancy [16–18]. The distinct molecular signatures displayed by enriched populations of stromal cells underlying epithelial cell populations from normal breast tissue and invasive cancer [19,20] provide a convincing molecular rationale for the stromal compartment as instrumental to tumor progression. Increased understanding of the contribution of underlying stroma to breast cancer, predominantly an epithelial cell phenomenon, provides exciting potential for manipulating the mammary stromal compartment in the development of therapy [15,21]. Given the emerging evidence for dietary contribution to breast cancer risk [22] through diet-mediated regulation of mammary epithelial differentiation, proliferation and apoptosis [23–27] coupled with the recognition that mammary fate and ductal development are controlled to a large extent by mammary fibroblastic and adipocyte mesenchyme [15], the prospect that diet-associated components may equally influence mammary stromal biology to influence the course of differentiation or neoplastic growth of the mammary epithelium is not far-fetched.

The invitation to write this minireview was prompted by our findings that mammary stromal adipocytes are early biological targets of dietary factors, specifically of the major isoflavone genistein (GEN) *in vivo* [27]. In that report, we showed that limited exposure (i.e., *in utero* and lactational only) of female rat offspring to a maternal diet containing soy protein isolate (SPI) as major protein source resulted in mammary stromal adipocyte-specific genomic changes (e.g., lipogenic gene expression) coincident with increased differentiation of mammary tissues that were distinct from those exposed to the control diet with casein as the major protein source. Further, we showed that the functional consequence of SPI-mediated adipocyte metabolic changes on neighboring mammary epithelium *in vivo* can be recapitulated by GEN *in vitro* through direct actions on differentiated 3T3-L1 adipocytes, a function likely related to their increased secretion of the adipokine adiponectin with GEN treatment [27]. Little is known of the gene pathways and mechanisms by which specific dietary factors may target the stromal compartment to promote breast health. We begin this review by highlighting seminal information on cell signaling mechanisms underlying mammary tumor protection by dietary factors. Next, we describe how mammary stromal remodeling has been implicated in underlying epithelial biology, with a focus on the emerging links between mammary adiposity and mammary ductal development as an indication of adipose-directed signaling. Finally, we discuss recently described, albeit limited, information on stromal-localized molecular targets of dietary factors, which may serve as paracrine mediators of dietary factor action on mammary epithelial cells.

2. Dietary factors and mammary epithelial targets in breast cancer protection

The incidence of breast cancer is high in the United States [1], with an increasing trend noted globally [28], yet strategies addressing its prevention remain extremely limited. Indeed, the current emphasis on the clinical management and treatment of breast cancer dramatically contrasts with the inadequacy of efforts directed toward disease prevention. In addition, there is reluctance among the general populace to embrace the concept that nutrition and lifestyle constitute highly modifiable risk factors for the prevention of breast cancer. In part, this may be due to the oftentimes conflicting reports, based largely on epidemiological studies, of the protective health benefits of specific diets. For example, high dietary fat intake, especially high polyunsaturated fatty acids, has been linked to the promotion of breast cancer in animal models [29,30] but currently not in humans [31,32]. On the other hand, saturated fat consumption is linked to breast cancer in women, but this has not been conclusively demonstrated in animal studies [33]. Similarly, dietary vitamin A, carotenoid and Vitamin D intake has been individually shown to prevent breast cancer in a number of human and animal studies, although a unifying outcome remains lacking [34,35]. The differences in physiological status of human subjects (prepubertal and post-pubertal; premenopausal and postmenopausal), source of dietary factors (from foods or supplements) as well as varying doses and 'developmental window' of dietary exposure in the many studies described in the literature [22,32,36] had preempted conclusive indications of the breast cancer-preventive benefits of consumption of any dietary factor. While studies with animal models and cell lines have been faulted for their simplistic approach toward understanding dietary prevention of breast cancer susceptibility, given the heterogeneity of the human population, these models have been invaluable in providing mechanistic insights regarding the contributions of specific bioactive components to breast cancer risk.

Efforts to understand the mechanisms underlying the breast cancer-preventive effects of dietary factors have focused on their

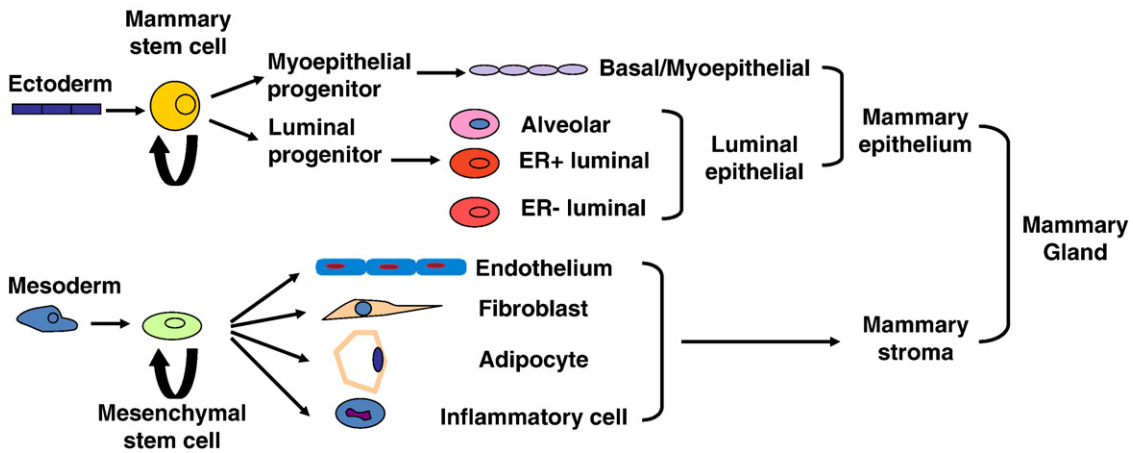

Fig. 1. The origin and lineage of the different cell types in the mammary gland. The mammary epithelium (luminal and myoepithelial) is embedded in the complex stromal matrix (also designated mammary fat pad) composed predominantly of fibroblasts, adipocytes and immune cells. The complexity of the mammary gland is a function of its distinct constituent cell types, which are subject to different endocrine and local regulation and which exhibit diverse functions. ER+ve, estrogen receptor positive; ER−ve, estrogen receptor negative.

biological and genomic consequences on mammary epithelial cells, where breast cancer arises. In particular, curcumin from turmeric [37], resveratrol from grape [38], capsaicin from chili pepper [39], flavonoids such as hesperetin and naringenin in citrus fruits and tomatoes [40], isoflavones (e.g., GEN, daidzein) from legumes and red clover [41,42] and epigallocatechin-3-gallate from green tea [43] have been demonstrated to provide different levels of preventive effects in rodent and cell culture models. An extensive discussion of the literature on the numerous mechanisms reported to underlie dietary prevention of breast cancer is beyond the scope of this current review, given the excellent recent reviews on this subject [44–48]. Suffice it to say that common mechanisms of actions have emerged: these include carcinogen activation/detoxification by metabolic enzymes, increased antioxidant and anti-inflammatory effects, induction of cell cycle arrest and inhibition of cell proliferation, decreased cell survival, enhancement of differentiation, increased expression and functional activation of various genes and corresponding proteins that are involved in DNA damage repair, tumor suppression and angiogenesis and down-regulation of oncogenes. Importantly, while the signaling pathways affected by various dietary factors in mammary epithelial cells are numerous, these pathways are interrelated, not mutually exclusive and as expected, utilize similar sets of genes previously elaborated in other tumor types [49].

Global gene expression profiling of mammary epithelial cells and subsequent functional annotation of gene expression changes have proven to be an effective tool for the discovery of novel pathways mediating dietary factor protection of mammary tumorigenesis. In studies from our laboratory using Affymetrix GeneChip microarrays [50], we showed a very low percentage of epithelial genes (~0.5% of 14,000 genes evaluated) whose expression is altered by exposure to either SPI or GEN diet beginning *in utero* to early adult stage (postnatal day 50), relative to control casein diet. The functional association of these identified genes with signaling pathways involved in immune response, protein and carbohydrate metabolism, growth regulation and stem cell niche (e.g., Wnt and Notch pathways) has provided invaluable insights into important targets of SPI-associated bioactive components and, in particular, GEN to induce epithelial changes for increased resistance to carcinogenic agents [51,52]. Indeed, our independent identification of the tumor suppressor *PTEN* [53] and of E-cadherin/Wnt/β-catenin signaling [54] as molecular pathways influenced by dietary exposure to SPI and GEN *in vivo* and by GEN *in vitro* has been bolstered by the recently elaborated linkage between these two signaling pathways in the regulation of normal and malignant mammary stem/progenitor cells *in vivo* and *in vitro* [55]. Similar support has been provided by other published studies, including those for epigallocatechin-3-gallate [56], phytoestrogens [57] and polyunsaturated fatty acids [58]. Taken together, the cellular pathways mediating dietary factor actions in the context of mammary epithelial growth regulation implicate their collective opposing actions on the expression and/or activity of tumor suppressors and oncogenes and their respective downstream targets.

3. Mammary stromal signaling in breast cancer prevention

How does the mammary stroma compartment potentiate resistance of its neighboring preneoplastic cells to tumor-initiating events? Much insight has emerged from studies on carcinoma-associated stromal fibroblasts, which can transdifferentiate into myofibroblasts and which have been demonstrated to promote primary tumor growth in human xenograft models when compared to noncancerous stromas [19,20]. The altered activity of tumor-associated stromal fibroblastic cells was associated with genetic and epigenetic alterations in specific gene subsets including that of the tumor suppressor *p53*, leading to increased expression of growth factors, cytokines and extracellular matrix components and which, by paracrine signaling, promoted neoangiogenesis and epithelial-to-mesenchymal transition in neighboring cells [19,59]. In an elegant recent study by Trimboli et al. [60], the conditional inactivation of the tumor suppressor *PTEN* in stromal fibroblasts of mouse mammary glands was shown to promote the initiation, progression and malignant transformation of mammary epithelium. *PTEN* loss was linked to increased extracellular matrix component deposition and innate immune infiltration, two key events associated with tumor malignancy and with activation of Ras, JNK and Akt growth-regulatory pathways [60]. This and similar studies [61–63] strongly support the notion that altered signaling in the tumor stroma, in this case, stromal fibroblasts, elicits aberrant epithelial growth regulation, leading to tumor manifestation.

Adipocytes constitute a significant component of the mammary stromal compartment and, similar to fibroblasts, are considered essential for mammary tumor growth and survival. While the mouse mammary fat pad consists primarily of adipocytes, this is not the case for the human mammary gland, where the developing mammary epithelium is closely sheathed by stromal fibroblasts. Nevertheless, the proximity of adipocytes to the epithelium and their high secretome activity [64,65] suggest significant influence. Indeed, the findings that (1) obesity, a disorder arising from altered gene–nutrient interactions, is a risk factor for breast cancer development [66], (2) diet-induced obesity in mice results in enlarged mammary glands and suppression of normal ductal development [67], and (3) adipose tissue from obese human subjects synthesize high and low levels of the adipokines leptin and adiponectin, respectively [68,69], which display opposing effects (promotion by leptin; inhibition by adiponectin) on mammary epithelial proliferation and which have been associated with regulation of mammary tumor development in mice [70], provide strong support for the influence of mammary adipocytes on breast cancer progression.

Interestingly, despite the increasing focus on obesity and nutrition/diet as major determinants of mammary epithelial oncogenesis, the connection between dietary factors with putative mammary tumor-protective effects and normal mammary adipose tissue biology has not been directly demonstrated. Two studies have recently appeared that highlight this association, albeit indirectly. Cho et al. [71] reported that the polyphenol (−)-catechin, among the many polyphenols present in green tea, enhanced the expression and secretion of adiponectin in 3T3-L1 adipocytes *in vitro*. The increase in adiponectin secretion by (−)-catechin was accompanied by increased insulin-dependent glucose uptake in differentiated adipocytes and decreased expression of the transcription factor Kruppel-like 7, which inhibits adiponectin expression [71]. While these *in vitro* findings did not directly address the consequence(s) of (−)-catechin promotion of adiponectin expression and secretion on mammary epithelial growth regulation, they are consistent with previous indications that green tea extracts have antiobesogenic activity [72] and inhibit mammary tumor initiation and progression in animal models of breast cancer [73]. In the second study by our group [27], we incorporated *in vivo* and *in vitro* strategies to link genomic and functional consequences in rat mammary glands upon *in utero*/lactational exposure to dietary SPI with paracrine signals from GEN-treated 3T3-L1 adipocytes to induce mammary epithelial differentiation. While our studies did not identify the paracrine signal(s) mediating the enhanced differentiation of mammary epithelial cells, we posited that one likely candidate is adiponectin, given the increased secretion of this adipokine in differentiated adipocytes treated with GEN at physiological doses [27]. Preliminary findings provide support to the latter, based on the higher adiponectin protein levels in the mammary glands of young adult female rat offspring exposed to SPI following the above dietary regimen, in the absence of changes in systemic levels of this adipokine (O. Rahal and R.C.M. Simmen, unpublished observations). Given that early only and

lifelong exposure to soy-enriched diets are mammary tumor-preventive in rodent models of carcinogenesis [52,74], findings that were borne out by epidemiological studies [75], the 'chicken-or-the-egg" question as to which mammary compartment (stromal or epithelial) is initially targeted by dietary factors to achieve the final outcome of increased mammary epithelial differentiation for decreased sensitivity to oncogenic agents, may constitute a fruitful direction for future investigation.

While the aforementioned studies investigated aspects of dietary influences on lipogenic and adipogenic regulators in the mammary adipocyte, mechanisms for dietary regulation at the level of adipocyte differentiation are also plausible. A great deal of our understanding of the molecular basis of adipocyte differentiation has been gained from studies of clonal fibroblastic preadipocyte cell lines (3T3-L1, 3T3-442A) and *ex vivo* studies of stromal vascular cells isolated from animals [76,77]. Committed preadipocytes, upon hormonal induction *in vitro* and via elusive *in vivo* signals, begin the differentiation program involving CREB-mediated phosphorylation of the transcription factor CAAAT-enhancer binding protein-β [77–79], followed by mitotic clonal expansion and activation of CAAAT-enhancer binding protein-α and peroxisome proliferator-activated receptor (PPAR)-γ. These, along with the sterol regulatory element binding protein-1c, transactivate a number of adipocyte-specific genes that maintain the adipocyte phenotype [80,81]. Throughout life, adipose tissue mass is regulated by a balance between formation (via hypertrophy of existing adipocytes and hyperplasia) and lipolysis. While the molecular events underlying adipocyte differentiation from precursor cells have been extensively studied, the precise origins of the adipose tissue *in vivo* are still poorly understood. In this context, two important recent advances in our understanding are noteworthy. First, using novel PPAR-γ reporter mouse strains (PPAR-γ-Rosa26 reporter and PPAR-γ-TRE-H2B-GFP) where endogenous PPAR-γ promoter leads to indelible marking of daughter cells with LacZ or GFP, Tang et al. [82], performed cell lineage tracing experiments. These elegant studies revealed that most adipocytes reside in the mural cell compartment in close proximity to the adipose vasculature and are already committed to an adipocyte fate *in utero* or early postnatal life. The second major advance in this area has been the identification of early adipocyte progenitor cells in the adipose tissue using flow cytometry. Using fluorescence-activated cell sorting, Rodeheffer et al. [83] identified cells that are $Lin^{-}CD29^{+}CD34^{+}Sca1^{+}CD24^{+}$ residing in the adipose tissue and that likely represent early adipocyte precursors since they can reconstitute a normal adipose tissue when injected into 'fat-less' lipodystrophic mice. It should be noted that the origin of adipocytes in the mammary fat pad has not been examined to date. In light of these studies, it is important to begin to address whether diet/dietary factor-associated cancer protection may be linked with altered commitment/differentiation of mammary preadipocytes.

4. Dietary factors and candidate mammary stromal targets for breast cancer prevention

While there is a paucity of information to directly link the targeting of specific mammary stromal cell types by known dietary factors to neighboring mammary epithelial growth regulation, a few candidate mediators have emerged. The most relevant are the adipokines adiponectin and leptin, which, because of their mammary adipocyte source, demonstrated regulation of mammary epithelial proliferation, differentiation and apoptosis though distinct mechanisms [70,84–86], and the negative and positive association of their expression levels, respectively, with breast cancer risk and adiposity [87–89]. *In vitro*, the isoflavone GEN has been shown to enhance secretion (hence, availability as endocrine/paracrine signals) of adiponectin [27] and to inhibit that of leptin [90]. The bioactive component chitosan from edible mushrooms, which was found to demonstrate antiobesogenic activity in rats [91], similarly reduced visceral adipose tissue leptin levels in mice consuming chitosan-supplemented diet [92]. Further, the short-chain fatty acid propionic acid, which is produced by the colonic fermentation of dietary fiber known to be preventive for the development of obesity [93], was shown to increase leptin messenger RNA expression and corresponding protein secretion, in the absence of coincident effects on adiponectin, in human omental and subcutaneous adipose tissue explants [94]. While the increased secretion of leptin by propionic acid appears counterintuitive to its antiobesity and, by extension, anticipated antimammary tumorigenic effects, this was accompanied by the reduced expression of the proinflammatory factor adipokine resistin, suggesting that the repertoire of adipokines presented to target cells may predict the final growth/proliferative outcome. In this regard, a recent study has shown significantly elevated plasma resistin levels in patients with breast cancer relative to those without disease [95], consistent with the link between inflammation and breast cancer risk.

Our group's approach to mechanistically address the directional signaling from stromal to epithelial cells initiated by bioactive dietary factor targeting of mammary fat pad involves (1) defining the *in vivo* measures of mammary epithelial and stromal differentiation upon early dietary SPI exposure and (2) recapitulating these responses in nontumorigenic mammary epithelial cells exposed to conditioned medium from differentiated 3T3-L1 adipocyte treated with GEN *in vitro* [27]. While our experiments constitute proof of concept, there are caveats that require further scrutiny. Our studies did not unequivocally identify GEN-specific gene targets in stromal fibroblasts and adipocytes distinct from those of epithelial cells, since the gene expression analyses were carried out using whole mammary tissues. Moreover, the biological and molecular outcomes observed *in vitro* with GEN precluded the contribution of other SPI-associated bioactive components, which may elicit more direct effects than could be attributed to GEN alone. Finally, it was not possible to demonstrate the converse directional signaling (i.e., from epithelial to stromal compartment) that may equally underlie mammary tumor prevention. In support of the existence of epithelial-to-stromal dialog, it was shown that during the development of breast cancer, the stromal compartment responded to signals from tumorigenic cells, leading to a more 'reactive' stroma and amplification of the tumorigenic state [96]. Additional studies using isolated adipocytes and fibroblastic cells derived from mammary fat pad or *in vivo* sampling of mammary fat pad followed by proteomic analyses [65,97], as a function of whole diets and purified bioactive components, will provide a 'glimpse' of the mammary secretome and presumably regulators of mammary stromal-mediated epithelial changes.

The elegant study by Lam et al. [70] demonstrating the precise role of adiponectin in mammary carcinogenesis can serve as a paradigm for mechanistically elucidating the role of adipocyte-specific gene targets of diet and dietary factors on mammary tumor prevention. In that study, MMTV-polyomavirus middle T-antigen transgenic mice with reduced adiponectin expression were generated to test the effects of adiponectin haploinsufficiency on the promotion of mammary tumors. Similar kinds of studies could be performed to test the function of candidate mammary adipocyte genes that are identified from gene expression analyses of tissues from rodent models under different dietary programs. In this regard, the recent report on the characterization of a 5.4-kb adiponectin promoter/5′ regulatory region that confers adipocyte-specific expression of target genes may provide an avenue for studying gene function in the context of bidirectional signaling in the mammary gland [98]. While it is unknown whether mammary adipose tissue exhibits specialized responses to extracellular signals or displays gene expression patterns distinct from retroperitoneal (subcutaneous) adipose tissue, an earlier study showed that the lipid composition in adipose tissue of virgin rat mammary glands resemble that of the retroperitoneal adipose [99].

5. Concluding remarks

The notion that the mammary fat pad is a direct target of bioactive dietary factors for mammary tumor protection is not difficult to envision, given that in any biological system, nothing stands alone. It is perhaps paradoxical that studies to address this remain relatively limited and the concept that bidirectional signaling within the mammary microenvironment for breast cancer prevention remains an intriguing observation. While the stromal compartment is not the main target of carcinogens [100], the possibility that a very early event upon carcinogenic insult is the sensing by stromal cells of 'something amiss' in adjacent epithelial cells is not unlikely. If this is the case, the identification of mammary fibroblast- and adipocyte-specific 'early' molecular targets by bioactive components in model systems may eventually provide biomarkers for the very early stages of the disease. The recent characterization of a mammary stromal fibroblastic cell line from mice that can differentiate to a preadipocyte lineage [101] in coculture studies with nontumorigenic or tumorigenic mammary epithelial cells will enable a proof-of-principle evaluation of the epithelial/stromal adipocyte dialog and associated mediators.

The findings that mammary stroma can reprogram testicular and neural stem cells to produce progeny committed to a mammary epithelial cell fate [102,103] and that a precancerous mammary stem cell may be programmed to become breast cancer [104] suggest the possibility that direct dietary factor effects on mammary stroma may alter stem cell behavior to inhibit neoplastic transformation. Thus, while mammary stem cells may constitute direct targets of bioactive dietary components as recently suggested by the report that curcumin added *in vitro* can induce mammosphere-forming ability in normal and malignant breast cells [105], a dual effect of dietary factors on mesenchymal and epithelial stem cells is also likely.

Further, dietary factors may directly influence the stem cell compartment in mammary stroma at the levels of the preadipocyte pool and the number of multipotent stem cells that enter the adipocyte lineage. The effects of obesity, high fat diets and other dietary factors on mammary preadipocyte populations remain unknown. It has been suggested that the inability of a particular adipose depot to expand may be causative in the accumulation of hypertrophic adipocytes and a predisposing factor in metabolic disease. Hence, it is possible that certain diets or dietary factors may mediate indirect beneficial actions on mammary epithelial cells via their modulation of preadipocyte commitment and/or differentiation of new mammary adipocytes. A recent report that *in utero* exposure to the environmental agent tributylin induced multipotent stem cells to differentiate into adipocytes provides strong support to this possibility [106].

Finally, while the contribution of inflammatory/immune cells found in mammary stroma is not included in the present review, their relevance as dietary factor targets to mediate epithelial proliferation and differentiation cannot be ignored, given that local inflammation associated with solid tumors is partly a consequence of immune cells in the tumor stroma [107]. Indeed, we observed that immune-related genes constitute major targets of dietary exposure to SPI and GEN in mammary epithelial cells of young adult rats [50]. The down-regulated expression of epithelial genes involved in antigen presentation, antigen processing and inflammation, including that of interleukin 17β, a homolog of interleukin 17, which is linked to neutrophil chemotaxis, suggests the possibility of similar specific targeting of immune cells localized

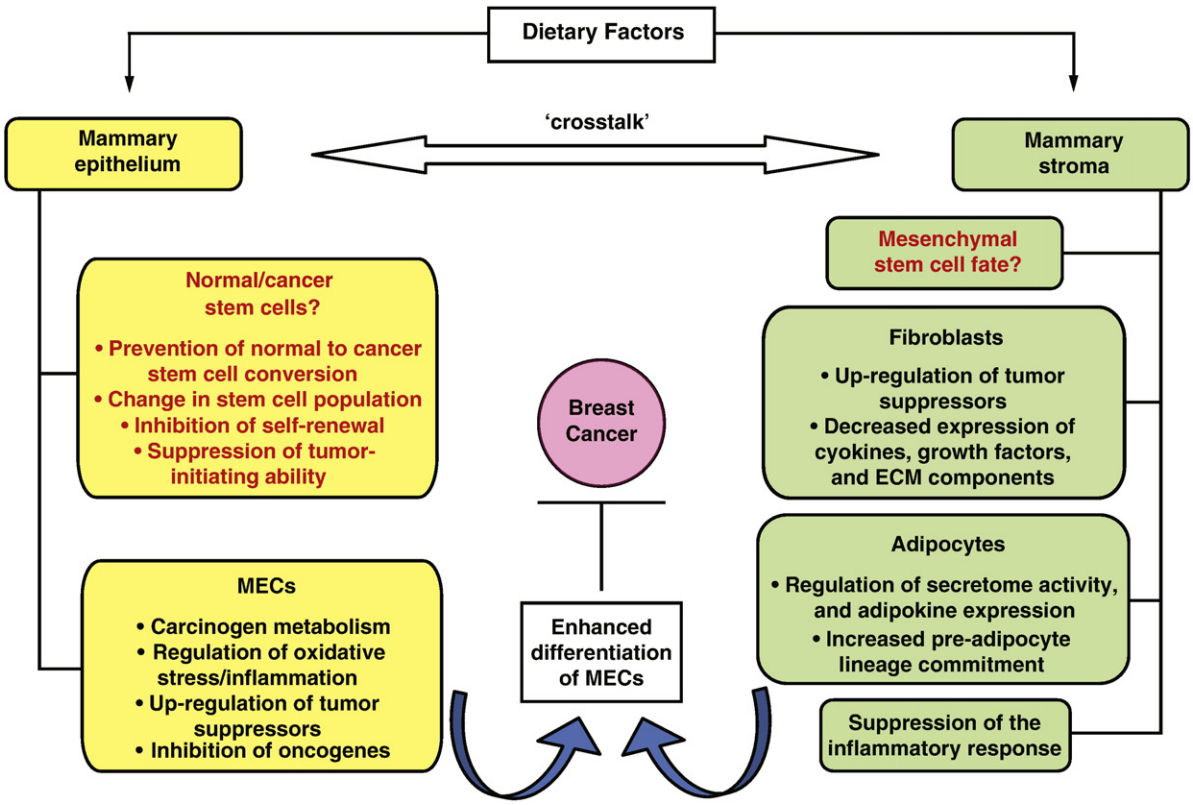

Fig. 2. A proposed model of cellular processes regulated by dietary factors in mammary epithelial and stromal compartments for breast cancer protection. The bidirectional arrows indicate an ongoing dialog between the mammary compartments. Mammary epithelial and mesenchymal stem cells are considered to represent cells of origin for each compartment. The composite actions of each mammary cell type result in the enhanced differentiation and, hence, increased resistance of mammary epithelial cells to carcinogenic insults, leading to decreased breast cancer risk.

to stroma and is consistent with promotion by the immune microenvironment of tumor progression [107].

In summary, bidirectional signaling between mammary stroma and epithelial cells promoted by bioactive dietary components constitutes a relevant biological event for mammary tumor prevention (Fig. 2). Thus, it is essential that, in future studies where dietary factor effects are described for mammary tumor prevention, their contributions to the phenotype and molecular profiles of mammary stromal fibroblasts and adipocytes are investigated coincident with those of neighboring epithelium. Gaining a better understanding of the complex interrelationships among the different mammary compartments in response to environmental ('dietary') cues may expand nutritional strategies for breast cancer prevention and therapeutic interventions.

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