

Cell of Origin of Breast Cancer: An Updated Hypothesis Merging Epidemiological Data with Molecular Biology

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Abstract

Two different hypotheses about cell of origin of breast cancer have been proposed. One theory states that breast cancer originates from an epithelial stem cell and subsequent genetic changes determine the phenotype, while another hypothesis postulates that breast cancer could originate from different cells, both stem cells and progenitor cells. Therefore, the phenotype in the latter situation is partly dependent on the differentiation of the epithelial cell of origin. Based initially on epidemiological data new research for instance gene expression arrays and gene transfection models supports the theory postulating that tumour biology of a breast cancer at least partly reflects the biology of the tissue/epithelial cell of origin at the time of initiation. It may be that the different theories actually not oppose each other and that tumours may develop from different precursor cells such as sometimes from a stem cell and sometimes from differently developed progenitor cells. The type of the mutations acquired, and/or the differentiation potential of the cancer cells, and the cell of origin are likely to decide whether a tumor follows a Cancer Stem Cell (CSC) model.

However, there are still unanswered questions that need to be addressed by further research to especially understand the hierarchy of differentiation of normal and tumour tissue.

Keywords: Breast cancer; Cancer stem cell; p53 cells; ER-tumours

Introduction

Different theories have been put forward on the normal cellular origin of breast cancer. One theory has stated that all breast cancer originates from a stem cell and successive genetic changes determine the phenotype of the cancer. Another theory, early proposed by our research group [1], suggests that the breast tumours stem from different progenitor cells and that the phenotype of the tumour at least partly is related to the differentiation/normal phenotype of the progenitor cell. This theory was strongly supported by epidemiological data on hereditary breast cancer syndromes and hormone related risk factors linked with tumour biology data. As such, already in 1989, we proposed that ER-tumours originated from an ER-normal cell, while ER+ tumours developed from ER+ normal cell counterparts [2]. The theory, refined in year 2000, was built on data preceding molecular data from expression analysis. It was further developed in relation to hereditary breast cancer and its tumour biology and clinical age presentation [3]. This review summarizes recent data shedding further light on the hypotheses by discussing experimental and human data from observational studies especially incorporating molecular and gene expression studies.

Observations in Mice and Man

Recently gene expression data has been added to theories on breast cancer histiogenesis depicting different tumour groups with common expression patterns proposed to reflect histiogenesis from different normal cell types. As such a luminal type A, a luminal type B, a Her-2 neu expressing type, a normal-breast tissue like type and a basal cell type have been defined. While no universal stem cell marker has been defined for the human breast epithelium or breast cancer, markers can be used to enrich a cell population harbouring a possible human stem cell, such as by CD44+/CD24-, CD133+, Lin-CD29highCD24high or ALDH1 positive cells [4] as it is possible to reconstitute a full ductal structure in serial passages. Further by immunohistochemical methods using different antibodies for cytokeratins, tumour histiogenesis

has been related to normal duct cell counterparts [5-7]. Studying cell division of normal breast ducts it is clear that mitoses are seen among all cell layers of the duct [8]. As ability to enter the cell cycle and undergo mitosis is a prerequisite for neoplastic transformation, these data suggest that tumours can originate from each cell layer and from different progenitor cells such as basal, luminal cell A and B. However the relative contribution of each cell type for neoplastic transformation may differ, suggesting that transformation early in life may give more undifferentiated tumour cells [1]. These tumours are possibly more apt to originate from basal cells compared with later in life.

Some data for human breast cancer exist for latency time (first initiating event to breast cancer diagnosis), Using data from radiation associated breast cancer average latency time approximates 24 years (range 8-40 years) [9]. Latency time in breast cancer can be estimated by tumour proliferation rate and age at diagnosis [9]. As tumour proliferation rate is generally higher in younger patients a shorter latency time is proposed for younger patients [9].

Other data also need to be recognized. Russo et al. have proposed by expanding a theory from mice that the differentiation of the breast epithelium, by defining 4 types or ductal patterns (lobules I-IV), reflects susceptibility for carcinogenesis [10]. Lobules I and II being more undifferentiated and more apt to neoplastic transformation.

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SEER data studied by Anderson and Matsuno on breast cancer incidence for different histologic tumour types clearly suggest the existence of least two main tumour groups characterized by an ER- and ER+ tumour type with different incidence pattern in relation to age [11]. By using different histology types of breast cancer they fitted the incidence into two main types of curves, one ER-premenopausal peak and one ER+ mainly postmenopausal peak [12].

Introducing identical oncogenes into different breast epithelial cells caused development of tumours with different phenotypes, again implicating the importance of the cell of origin for the phenotype [13]. This strongly supports the previously presented theory that the tumour phenotype at least partly is related to the cell of origin [1]. The same researchers also have found that the cell of origin also determines the metastatic potential of the tumour [13]. The proteins EZH2 and BMI1 have a role in breast stem cell regulation, EZH2 overexpression correlates with a poor prognosis in breast cancer while BMI1 overexpression correlates with a good outcome [14]. This also may reflect transformation of different cell types and the importance of cell of origin. However, it needs to be recognized that accumulated somatic mutations is of great importance in determining tumor phenotype as described by Cahill et al. [15] and Fearon and Vogelstein [16]. Accumulated somatic mutations explain therefore to a large part observed differences between tumors during tumor progression.

Using gene expression data a new taxonomy of breast cancer has been developed defining a claudin low type, basal type, her-2 neu type, normal like, luminal A and luminal B type [17-19]. In Figures 1-3 different risk factors (environmental and genetic) of breast cancer and histologic types have been depicted in relation to histogenetic subtype suggested from the above references.

As such tumours in patients with BRCA1 associated breast cancer is correlated with the basal type of breast cancer while tumours in BRCA2 carriers show a stronger correlation with luminal tumours [20,21]. Using comparative genomic hybridisation BRCA1 tumors had a higher frequency of copy number alterations than sporadic breast cancers (P=0.00078) [22]. In particular, frequent losses on 4p, 4q, and 5q in BRCA1 tumors and frequent gains on 7p and 17q24 in BRCA2 tumors distinguish these from sporadic tumors. Distinct amplicons at

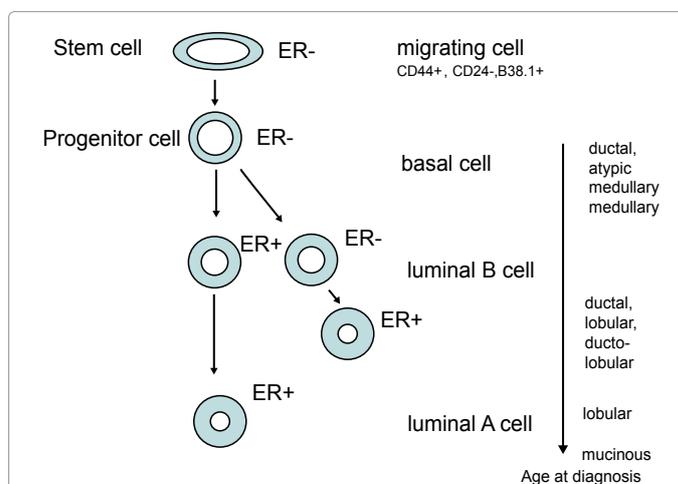


Figure 2: Suggested hierarchical order of breast cancer cell types (cell of origin) defined by expression analysis in relation to hormone receptor status, histological subtypes and age at diagnosis.

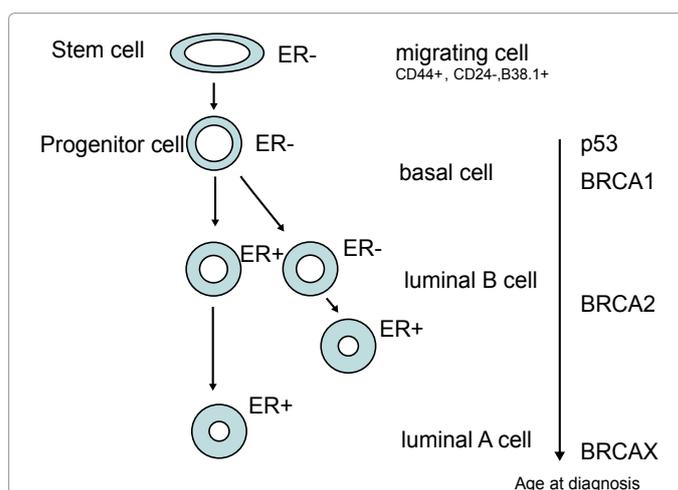


Figure 3: Suggested hierarchical order of breast cancer cell types (cell of origin) defined by expression analysis in relation to hormone receptor status. In the figure also is hypothesized where tumours developing in germline mutations carriers of p53, BRCA1, BRCA2 and BRCA3 preferentially have its cell of origin. The hypothesis postulates that tumours originating in germline mutation carriers of BRCA1 mainly are ER-, in BRCA2 carriers mixed ER+ and ER- and in BRCA3 carriers mainly ER+. The origin of the BRCA1 tumors recently has been associated with a luminal progenitor cell instead of a basal located stem cell (19) although by gene expression studies BRCA1 associated tumors display a basal phenotype. The cell of origin is also related to age at diagnosis with receptor positive tumours initiated at a higher age in a more terminally differentiated tissue.

3q27.1-q27.3 were identified in BRCA1 tumors and at 17q23.3-q24.2 in BRCA2 tumors.

It has been suggested that the basal-like-, ERBB2- and luminal B-sporadic and familial tumour subtypes have an ER-negative breast stem/progenitor cell origin, whereas luminal A tumours arise from an ER-positive progenitor cell, supporting a hierarchical breast carcinogenesis model, whereas crucial genomic imbalances are clonally selected during the tumour development [23].

Also data of methylation of breast cancer genes suggest that the methylation pattern reflect the methylation pattern present in normal

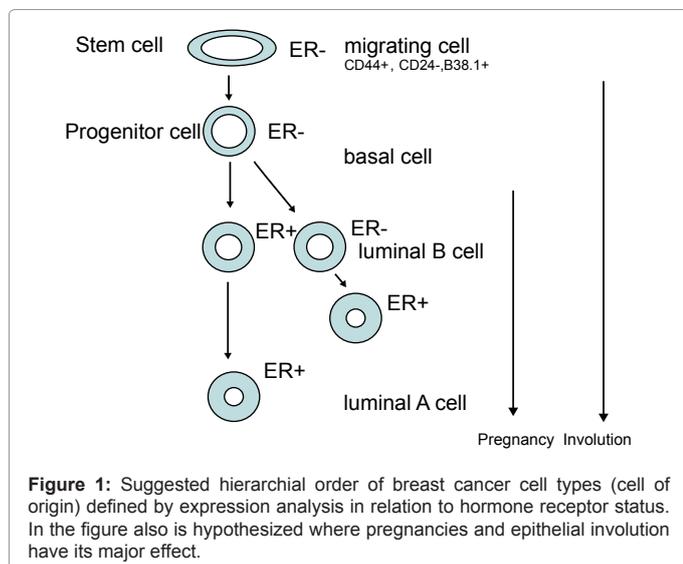


Figure 1: Suggested hierarchical order of breast cancer cell types (cell of origin) defined by expression analysis in relation to hormone receptor status. In the figure also is hypothesized where pregnancies and epithelial involution have its major effect.

breast epithelial tissue and thus could reflect the cell of origin [24]. In a recent publication this is further abrogated by the finding that the tissue of origin determines cancer-associated CpG island promoter hypermethylation patterns [25].

In mice keratin 6a depicts mammary bipotential progenitor cells that can give rise to a unique tumour model resembling the human counterpart normal-like breast cancer [26].

Studying the gene expression of normal human breast tissue researchers were able to define two distinct patterns. One pattern shared characteristics of stromal and stem cells with some features of mesenchymal and myoepithelial cells sharing many features of the claudin-low intrinsic breast cancer subtype [27]. These women also had a stronger family history of cancer and were more nulliparous than the second expression group.

Both in humans and in mice BRCA1 associated tumours are thought to originate from a luminal progenitor cell [28] despite initial expression studies suggested a basal origin. Typically BRCA1 associated breast cancer are estrogen receptor negative and progesterone receptor negative, p53 mutated and growing with pushing margins. A minor proportion of the tumours is estrogen receptor positive. Initially it was thought that these tumours may represent sporadic tumours appearing with age in mutation carriers. Recent work looking at tumour mutation patterns however, suggest that the estrogen negative tumours are caused by the BRCA1 status [29]. It thus may be that the most BRCA1 tumours are hormone receptor negative, while in BRCA2 only up to 50% of the tumours are receptor negative, and this may reflect that the cell of origin may have a different ability to differentiate into hormone receptor positivity.

In mice it has also been demonstrated that different mammary epithelial layers contain different long lived stem cells having a direct implication for the origin of tumours, supporting the notion that different tumours can originate from different host cells [30].

Mouse models have proven of great importance in addressing the cellular origin of cancers [31] such as transgenic or conditionally targeted gene technologies studying the effects of oncogenes and tumour suppressor genes and genetic alteration of cells *ex vivo* before evaluating their tumorigenic capacity in mice.

A unidirectional differentiation scheme of tissues from stem cell, progenitor cells to differentiated cells have been assumed, but new research data suggest that normal and neoplastic non stem cells can covert to a stem cell like state [32]. This finding may further complicate the possibility to eradicate cancer cells, having a stem cell characteristic, applying the Cancer Stem Cell (CSC) dogma into the clinic. Visvader [31] correctly argues that a distinction should be made to differentiate the cell of origin and CSC because in most instances the phenotype of the cell of origin may differ substantially from the CSC. The cell of origin being related to the initiating cell, while the CSC more is related to the propagation of the tumor. Further the CSC is not synonymous with a normal stem cell but more often represent a dedifferentiation of a progenitor cell [31,33]. Donnenberg et al. have emphasized that dedifferentiation as a feature of relapse and metastasis [33] and that tumor cells become more stem cell like when differentiation signaling pathways are blocked by gene deletions, environment or epigenetic reprogramming. A similar dedifferentiation has been described for central nervous system tumors were most differentiated cells upon genetic alterations could give rise to the heterogeneity of gliomas [34]. Markers for CSCs may be imperfect leading to wrong results of phenotypic switching using mathematical models [35]. However,

differences may exist between various tissues such as in tissues with cells that rapidly proliferate, e.g. the gut, cells may not live long enough to acquire mutations in progenitor cells and therefore easier could have a origin closer to a normal stem cell [31]. In the breast proliferation has been described in both luminal, intermediate and basal epithelial cell layers especially in terminal end bud, while in normal breast tissue from adult women proliferation is low or absent in ALDH+ cells, the cell population harbouring a proportion of normal stem cells [36]. The hypothesis could be raised that breast tumors initiated before or early in puberty could involve a cell of origin closer to a stem cell, while initiations later in life would more involve progenitor cells of different differentiations. We have from patients with radiation associated breast cancer described that the breast tumors more often were progesterone receptor positive if the radiation exposure took place after the first pregnancy than before [37]. This implies that a tumor initiated after the pregnancy could have a cell of origin from a more differentiated hormone receptor positive cell.

Synthesis

There is a need to recognize the breast as a dynamic organ with main development during puberty, but with ducts under cyclic hormone influence early in life through the menstrual cycle, and profoundly affected by pregnancy and lactation and with involution after menopause.

Do these different theories of breast cancer development contradict each other? The overwhelming data combining epidemiological data, tumour biology data and now gene and protein expression data suggest that the theory that all breast cancer originates from a common undifferentiated stem cell is wrong. However, if a theory is adopted that tumours may develop from different precursor cells such as sometimes from a stem cell and sometimes from different developed progenitor cells, most of the combined observational data would fit such theory.

It can also be hypothesized that tumours originating from migrating uncommitted stem cells need to be a rare event otherwise individuals would develop tumours early in life in many organs and this would seriously threaten human reproduction. However, a progenitor cell/stem cell, that is responsible for the breast duct development (lobe specific) having its major effect at or after puberty, during menstrual cycle and at pregnancies/lactation, could be responsible for tumour development in women, who already would have a chance of given birth to children, thus not seriously limiting human reproduction.

Also a combined theory recognizes that no phenotype is specific for a given etiological factor, as such a BRCA1 phenotype also can be shared with sporadic breast cancers having the BRCA1 gene silenced by epigenetic factors such as promotor methylation [38]. Further among women having BRCA1 germline mutations also ER+ tumours must occur especially as sporadic tumours late in life and due to the possibility that the cell of origin of BRCA1 tumours may partly be able to differentiate into ER+ tumours. Recent research indicates that ER+ and ER- BRCA1 associated breast cancers share molecular profiles although having different hormone receptor status [29,39].

Current HRT exposure, especially if given in a combined therapy of estrogen and progestin, renders the woman at a rather high risk for breast cancer especially after 4 years of exposure [40-43]. Slightly higher risks have been seen for ER+ tumours than for ER- tumours [44,45] and for lobular tumours than for ductal or medullary tumours [44,45]. Interestingly the breast cancer risk after estrogen only exposure is low or nonexistent [42,46]. Past exposure >5 years of combined

HRT is not associated with an increased risk for breast cancer [41,43] suggesting that the combined exposure affects an already transformed neoplastic cell that are triggered in growth by the hormone therapy. Therapy with longacting insulin such as Glargine, stimulating also the IGFR1 receptor, may have a similar promoting effect on breast cancer as an increased risk is seen in some studies after a short exposure time [47,48].

Also in other diseases, such as acute leukemia, the origin of the malignant cell has been discussed in a similar manner as in breast cancer [49,50].

Lander [51] by pointing out a number of inconsistencies stated that; "The traditional view of cell differentiation as a set of irreversible, deterministic transitions from one stable state to another is giving way to a view in which cell states are quasi-stable points on an 'energy landscape' along which cells move in response to both stochastic variation and external signals". We therefore need to have a very open mind that theories of organ evolution and tumour development ought to include components not presently recognized. Again the possibility of bidirectional development of stem cells needs to be taken into account [32].

However, defining breast cancer from its histogenesis, combining epidemiological data, tumor biology data and gene and protein expression data, is still fruitful and may help clinicians to develop individualized targeted therapies. At the moment it is unclear if both cell of origin and the mutation profile are of importance in determining the molecular and clinical heterogeneity of a tumor thus guiding the therapy [39]. Evidence suggest that CSCs are relatively resistant to radio- and chemotherapy. Novel therapy approaches for CSC-targeted therapies are therefore needed [52]. A number of novel agents aimed at targeting CSC are presently tested in preclinical and phase I-II trials tested. Targets include Notch, Hedgehog, BCL-2, CD44, EpCAM, retinoic acid receptor and rexinoid receptor and PARP [52]. Further it is reasonable to postulate that tumors developing from a more undifferentiated normal breast cell, while being more difficult to initially treat, may actually render some women long term survivors if therapy is successful. Therapy of the more differentiated tumors may, in a similar manner as in lymphoma, initially show a better prognosis while actually the patient group in the long run has a higher later mortality rate.

In conclusion the bulk of epidemiological and tumour biology data support a hypothesis that the biology of a breast cancer at least partly is related to the differentiation status of the cell origin of the normal breast epithelium.

In Figures 1-3 below the hypothetical origin of cells, tumour types, epidemiological risk factors (environmental and genetic) and hereditary syndromes are described in relation to normal cell of origin and hormone receptor content. In the figures the possibility of a common origin for myoepithelial cells and ductal epithelium through a bipotential comitted progenitor cells has been omitted. Likewise the normal like breast cancer subtype has not been included as more information is needed to understand its position in the histogenetic tree. Recently the origin of the BRCA1 tumor has been associated with a luminal progenitor cell instead of a basal located stem cell [19].

Conflict of Interest

The author has no actual or potential conflict of interest including any financial, personal or other relationships with people or organizations within that could inappropriately influence this work.

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