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REVIEW ARTICLE

NORMAL MAMMARY STEM CELLS VERSUS BREAST CANCER STEM CELLS: AN OVERVIEW

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ABSTRACT

In the past decades, there has been an increasing evidence for the existence of breast cancer among women worldwide. Despite the progress that has been made in the human breast cancer research, the origin of tumor, maintenance and its resistance to chemotherapy are poorly understood. However, it is already established that breast cancer may be originated and sustained by a small proportion of stem-like self-renewing cells called breast cancer stem cells. Therefore, understanding the role of stem cells in the normal human breast development and its carcinogenesis is crucial in attempts to differentiate the breast cancer stem cells from the bulk of a tumor. This review will focus on the mammary gland development, self-renewal and differentiation of normal breast stem cells, signaling pathways which regulate their self-renewal and differentiation, deregulation of these normal signaling pathways which might lead to the neoplastic conversion of the normal mammary stem/progenitor cells, how normal mammary stem and their progenitor cells are transformed into breast cancer stem cells, how do they interact with its tissue specific microenvironment, their cell surface markers to identify and target those breast cancer stem cells. Elucidation of these important points is essential to develop novel therapeutic strategies and to improve the current diagnostic techniques.

INTRODUCTION

According to 2013 Statistics from the Madras Metropolitan Tumor Registry at the Adyar Cancer Institute's hospital registry, a subtle change has taken place that has had breast cancer incidence growing at a much higher rate than cervical cancer in Tamil Nadu, Chennai in particular (The Hindu, 2013). Current Indian Council for Medical Research (ICMR) studies show that incidence of breast cancer has nearly doubled in the last 24 years. One in every 22 women is likely to suffer from breast cancer. The International Agency for Research on Cancer (IARC) has projected that India could see around 250,000 new cases by 2015 (Times of India, 2013)**.** American Cancer Society has reported that breast cancer is the most common noncutaneous cancer in U.S. women, with an estimated 226,870 new cases of invasive disease (plus 63,300 cases of *in situ* disease) and 39,510 deaths in 2012 (American Cancer Society, 2012**)**.

Despite the progress that has been made through the past two decades in the diagnostic techniques and treatment, breast cancer is still a leading cause of cancer related deaths among women. However, accumulating evidences suggest that mammary stem cells exist in the mammary gland, which give rise to mammary epithelial cells. It is also established that breast cancer may be originated and sustained by a small proportion of stem-like self-renewing cells called breast cancer stem cells. Therefore, understanding the role of stem cells in the normal human breast development and its carcinogenesis is crucial in attempts to identify the breast cancer stem cell population from the bulk of a tumor and target them specifically in order to prevent relapses and metastasis of the tumor. So, this review will focus on the mammary gland development, self-renewal and differentiation of normal breast stem cells, origin of tumor, signaling pathways which regulate their self renewal and differentiation, deregulation of these normal signaling pathways which might lead to the neoplastic conversion of the normal mammary stem/progenitor cells, how do they interact with its tissue specific microenvironment, their cell surface markers to identify and target those breast cancer stem cells. Elucidation of these important points is essential to develop novel therapeutic strategies and to improve the current diagnostic techniques (Fig 1).

MAMMARY GLAND DEVELOPMENT

The mammary gland in humans and in other mammals is a

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dynamic organ that undergoes significant developmental changes during pregnancy, lactation, and involution (Rudl and PS *et al*, 1997**).** As reported by various research groups, it is believed that the mammary system in mammals is comprised of a wide range of cell populations including differentiated cells of different lineages, undifferentiated multipotent stem and progenitor cells with self renewal and differentiation properties. In humans, the mammary epithelium consists of a network of ducts that form before birth, by branching and invading the mammary fat pad.

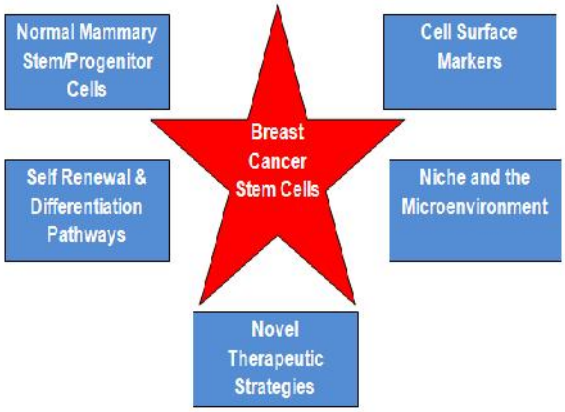

Figure 1 Normal Mammary Stem Cells versus Breast Cancer Stem Cells- Schema

Illustration depicting the key aspects of normal mammary stem cells and breast cancer stem cells

The ducts are formed by two epithelial cell types: a basal or outer layer of contractile myoepithelial cells surrounding an inner luminal layer of milk producing specialized epithelial cells (Rudl and PS *et al*, 1997 and Hennighausen L *et al*, 2001). After birth, mammary gland growth remains quiescent until puberty (Watson CJ *et al*, 2008). At puberty, ductal outgrowth rapidly increases under hormonal stimulation, resulting in side branching (Rudl and PS *et al*, 1997; Hennighausen L *et al*, 2001). The fundamental unit is based on actively growing grape-like structures called terminal ductal lobular unit (TDLU) (Capuco A.V *et al*, 2002). It is likely that the cellular repertoire of the human mammary gland is generated by a stem cell component. These stem cells have a unique capacity for self-renewal as well as for generating the three lineages that comprise the lobulo-alveolar structure of the adult gland: myoepithelial cells forming the basal layer of ducts and alveoli; ductal epithelial cells lining the lumen of ducts, and alveolar epithelial cells synthesizing milk proteins. Under the regulation of systemic hormones, as well as local stromal epithelial interactions, local growth factors, cellular/extracellular matrix, these cells proliferate extensively, differentiate during each pregnancy and lactation, and undergo apoptosis during mammary involution (Rudl and PS *et al*, 1997, Hennighausen L *et al*, 2001; Wiseman B S *et al*, 2002) (Fig 2).

MAMMARY STEM CELLS

In 1959, the existence of self-renewing, bipotent mammary stem cells was first demonstrated by the work of Deome KB *et al* using limiting dilution transplantation experiment. Their studies in mice showed that progenitor cells are capable of forming an entire mammary gland (Deome K *et al*, 1971). Further, this was supported by additional experimental evidences that when surgically removed random fragments of mammary epithelium were serially transplanted to cleared fat pad, they were able to generate a functional mammary gland (Deome K *et al*, 1971; Kim ND *et al*, 2000; Welm BE *et al*, 2002). In an attempt to isolate and purify mammary stem cells, it was shown that cells that expressed stem-cell antigen-1 (SCA)-1 enriched progenitor cells, were able to regenerate the mammary gland *in vivo* (Welm BE *et al*, 2002). Later, the multipotent epithelial cells in the normal adult breast were also characterized in which two distinct types of human breast epithelial cell (HBEC) progenitor population could be distinguished on the basis of their differential expression of their cell surface antigens. Luminal epithelial cells are phenotypically characterised by the expression of epithelial cell adhesion molecule (EpCAM) also known as epithelial surface antigen (ESA), mucine-1(MUC1), cytokeratin (CK) 7, CK8, CK18 and CK19 as well as oestrogen receptor (ER) and progesterone receptor (PgR) (Visvader JE *et al*, 2006; Latza U *et al*, 1990; Petersen OW *et al*, 1986). Myoepithelial cells are characterised by expression of common acute lymphoblastic leukaemia antigen (CALLA) or CD10, α6-Integrin or CD 49f, CD 29, CD 24, Thy-1, alpha-smooth muscle actin, vimentin, and CK5 and CK14 amongst others (Gudjonsson T *et al*, 2002; Taylor P J *et al*, 1989; Williams J M *et al*, 1983; Gugliotta P *et al*, 1988; Guelstein V *et al*, 1998; Gusterson B *et al*, 1986). It is also suggested that mammary stem cells with the phenotype Lin-$CD24^{+}CD29^{high}$ can generate a functional mammary gland (Shackleton M *et al*, 2006; Visvader JE *et al*, 2006).

Mammary stem cells have also been studied *in vitro* cell using a culture assay known as the neurosphere assay, that identifies undifferentiated human mammary stem cells grown in culture (Dontu G *et al*, 2003) known as mammospheres and to identify a candidate human breast cancer stem cells (Ponti D *et al*, 2005). These culture systems have shown that mammospheres exhibit stem cell-like functional properties of relative quiescence and phenotypic properties such as ESA, CK5, and α-6-integrin expression (Stingl J *et al*, 2005).

SIGNALING PATHWAYS

Research over the past has elucidated various signaling pathways that regulate the self-renewal of mammary stem cells. The pathways include Notch, Wnt and Hedgehog.

Notch

The Notch pathway has been shown to be involved in the normal development of the mammary gland. The Notch transmembrane receptor proteins are part of a signalling pathway that is critical for the correct developmental fate of cells and various tissues and are expressed in stem cells and early progenitor cells (Gaiano N *et al*, 2002). Notch signaling has been shown to play an important role in cell-fate determination, as well as in cell survival and proliferation (Miele L *et al*, 1999; Artavanis-Tsakonas S *et al*, 1999). Notch signaling is active in several distinct developmental stages of the mammary gland and that Notch acts as a regulator of asymmetric cell fate decisions. Notch activation promotes the self-renewal of stem cells, whereas in later stages of

development it biased cell fate decisions in mammary progenitor cells toward the adoption of a myoepithelial cell fate versus an epithelial cell fate (Dontu G *et al*, 2003)**.** It is also reported that *in vivo* transgenic mice which expressed a constitutively active form of Notch 4 in the mammary gland fail to develop secretory lobules during gestation, and subsequently develop mammary tumours (Soriano JV *et al*, 2000). Indeed, it has been detected that Notch family members are expressed in mammospheres, and thus the Notch ligands affect the self-renewal and differentiation of normal mammary epithelial cells. These findings support the role of Notch signaling pathway in promoting the self-renewal of mammary stem cells in normal breast development, and suggests that alterations in Notch 4 signalling might play a significant role in the transition of a healthy stem cell to a cancer stem cell.

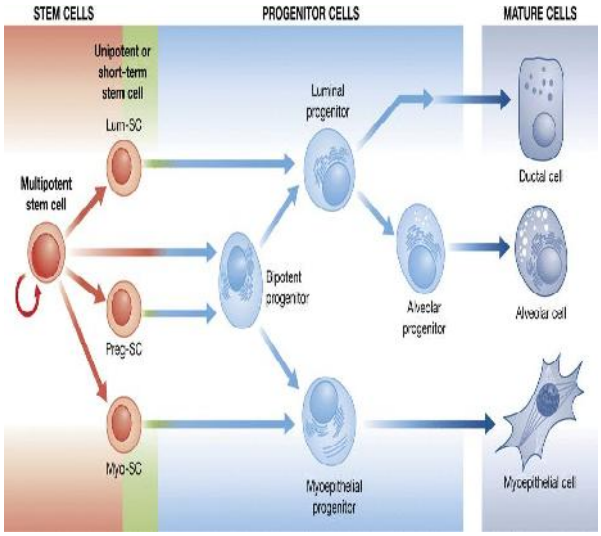

Figure 2 Epithelial Stem Cell Hierarchy

Differentiation patterns of mammary epithelial stem cells in to luminal, progenitor and myoepithelial cells. (Figure courtesy: Stemcell Technologies. www.stemcell.com)

Wnt

The Wnt pathway regulates cell fate determination in a number of tissues, including the mammary gland. The Wnts are a family of secreted proteins. So far, the most well characterized Wnt signaling pathway is called the canonical Wnt pathway, in which Wnt ligands signal through the stabilization of β-catenin (Veeman MT *et al*, 2003)**.** A pro-oncogenic role for β-catenin, a downstream target of Wnt signalling, has also been described. Wnt signalling has been shown to play a role in haematopoietic self-renewal, and experimental evidence from transgenic mouse models has shown that activation of the Wnt signalling pathway in stem cells can lead to epithelial tumours (Brittan M *et al*, 2002; Reya T *et al*, 2003).

Differential expression of molecules in the Wnt pathways have been identified in mammospheres, compared with differentiated cells, which suggests the possible involvement of the Wnt pathway members in the regulation of normal mammary stem-cell function. Furthermore, overexpressing Wnt in the mouse mammary gland increased mammary tumour formation (Schroeder JA *et al*, 2002)**.** Together, these data suggest that Wnt signaling is important in normal mammary gland development. Recent studies also suggest that Wnt signaling is associated with expansion of a multipotent progenitor cell population (Brennan KR *et al*, 2004).

Hedgehog

The hedgehog signaling pathway was first identified in *Drosophila*, where it is required for early embryo patterning (Cohen MM, 2003). This pathway occurs during the development of many organs, especially the mammary gland, and it regulates embryonic patterning, cell fate specification and regenerative stasis. The main components of the Hh signaling pathway include ligands (Sonic Hedgehog, Indian Hedgehog, and Desert Hedgehog), receptors (Patched-1 and Patched-2), effector (Smoothened), and transcription factors (Gli 1-3) (Lewis MT, 2001)**.** Recent studies have indicated that hedgehog signaling is important in embryonic mammary gland induction, ductal morphogenesis, and alveolar development. A critical role for hedgehog signaling in mediating epithelial stromal interactions during ductal development has been shown by the genetic analysis of two hedgehog signal transduction network genes, Ptch1 and Gli-2. Disruption of either gene leads to similar, yet distinct, defects in ductal morphogenesis that are mainly ductal dysplasias similar to the hyperplasias of the human breast (Suling Liu *et al*, 2005). Studies have shown that Hh signaling is involved in the interaction between the stroma and epithelial cells of the developing mammary gland during ductal morphogenesis and mammary epithelial stasis (Li N *et al*, 2008; Lewis MT *et al*, 2009)**.** Some components of the Hh signaling pathway are mutated or overexpressed in breast cancer (Lewis MT, 2001). There is evidence that altered hedgehog signaling has a direct role in the neoplastic progression of the mammary gland (Xie J *et al*, 1997).

BREAST CANCER STEM CELLS

Recent theories suggest that a small population of cells within some tumors possess the ability to self-renew and proliferate and are thus able to maintain the tumor. These cells are called as cancer stem cells (CSCs) or tumor-initiating cells. It is also suggested that cancers in epithelial organs, including the mammary gland, may result from deregulation of normal stem-cell functions, such as tightly regulated self-renewal and differentiation mechanisms. Another model postulates that cancer originates from mutations occurring in a few cells or a single cell that eventually leads to uncontrolled and unlimited proliferation of a population of cells (Nowell PC, 1976). Another model hypothesizes that adult mammary stem cells accumulate genetic changes leading to transformation over several years with the eventual development of solid tumours which inturn leads to the activation of proto-oncogenes into oncogenes and inactivation of various tumour-suppressor genes and ultimately giving rise to subtypes of cells in the tumour which have acquired several traits such as the ability to evade apoptosis, self-sufficiency in growth signalling, tissue invasion and metastasis, and limitless replicative potential (Hanahan D *et al*, 2000)**.** Some of the experimental observations have identified candidate stem cells that are Oestrogen positive (ER+). Indeed, ER+ stem cells have been identified as being important in adult mammary gland homeostasis (Clarke RB *et al*, 2005)**.** However, greater than two-thirds of breast tumours are ER+ and the majority of these tumours are dependent on

oestrogen for their growth (Buzdar A *et al*, 2004). A model of breast cancer origin has been proposed in which ER+ tumours are derived from ER+ stem cells or ER+ early or late progenitor cells and ER– tumours are derived from the more primitive ER– stem cells (Dontu G *et al*, 2004).

Like the normal mammary epithelial stem cells, certain surface markers are associated with breast cancer stem cells. Al-Hajj and colleagues in 2003 reported that a tumourigenic population of cells from primary human breast cancers were prospectively identified based on the expression of unique cell surface antigens. In that study, lineage-negative human breast cancer stem cells from the tumors were fractioned using FACS with respect to a combination of three additional markers: CD44, CD24 and ESA. These cells with the phenotype ESA+/CD44+/CD24_/low/lineage- when injected into the mammary fat pads of Non obese Diabetic/Severe Combined Immune Deficient(NOD/SCID) mice, as few as 200 cells with this phenotype consistently formed tumors (Al-Hajj *et al*, 2003). Perhaps CD44+ cells are predominately basal-like and therefore are present in poor prognosis basal-like tumors, whereas CD24– cells are luminal-like and therefore present in more differentiated luminal-type cancers. Therefore, a subpopulation of human mammary cancer cells bearing the phenotype ESA+CD44+CD24–/lowLineage– are identified as 'breast cancer stem cells' (BRCSCs) (Visvader JE *et al*, 2006; Stingl J *et al*, 2005)**.** It has been found that more than 95% of primary human breast carcinomas and all metastatic lesions are homogeneously positive for keratin K19. This is a remarkable observation in light of the heterogeneity of human breast carcinomas and supported the idea that breast cancer originates from normal keratin K19 positive luminal epithelial cells (Bartek J *et al*, 1985).

A recent study has showed that aldehyde dehydrogenase-1 (ALDH1), a detoxifying enzyme that may play a role in the differentiation of stem cells has been detected in a subpopulation of both normal and malignant human mammary epithelial cells exhibiting stem/progenitor cell properties. This subpopulation is tumorigenic, capable of self-renewal, and able to generate tumors that had the heterogeneity of the parental tumor (Ginestier C *et al*, 2007)**.** Further, Eddy et al in 2007 has demonstrated that Human Epidermal Receptor-2 (HER-2), a member of the epidermal growth factor receptor (EGFR) kinase family, is overexpressed on roughly 30% of breast tumours (Eddy *et al*, 2007). According to Korkaya *et al*, Over-expression of HER2 in breast cancer stem cells increased their invasive capacity and tumourgenicity when transplanted into NOD/SCID mice. Moreover, inhibition of HER2 significantly decreased the proportion of breast CSCs, decreased tumor forming capacity and decreased invasion (Korkaya *et al*, 2008). Together these studies indicate that breast CSC activity is regulated by HER2 and that this population can be depleted by HER2 inhibition.

Nevertheless, a study has reported that BRCA1 mutant cancer cell lines contained a subpopulation of CD24+CD29+ or CD24+CD49f+ cells that exhibited increased proliferation and colony forming ability in vitro, and enhanced tumor-forming ability in vivo (Atkinson RL *et al*, 2010). Another study shows that the *Brca1* mutation carriers had lower mammary stem cells (MaSC) numbers but higher numbers of luminal progenitors in normal glands. However, the progenitors from *Brca1* mutation carriers showed higher colony-forming ability than non-carriers suggesting an altered mammary hierarchy resulting from either stem or progenitor cell dysfunction (Athanassios Vassilopoulos *et al*, 2008). It has been shown that homing and migration pathways of haematopoietic/leukocyte cells might be involved in Breast Cancer Stem Cells and metastatic disease. CXC Chemokine Receptor 4 (CXCR4), a chemokine receptor expressed by haematopoietic stem cells which binds to CXC Chemokine Ligand 12 (CXCL12), has been shown to be increased by a factor of four in mammospheres and to be expressed in both metastatic breast cancer cells (Muller A *et al*, 2001)**.** Additionally, CXCR1 expression is also found higher in $ALDH^+$ cells from numerous breast cancer cells lines (Ginestier C *et al*, 2009)**.**

There is also evidence that Ptch1 mutation has been associated with human breast cancers (No well PC, 1976)**.** A natural polymorphism in the 3′ end of the Ptch1 coding region (C3944T; Pro1315→Leu) has been linked to increased breast cancer risk associated with oral contraceptive use (Chang-Claude J *et al*, 2003)**.** Also, there are various effectors mediating heterotypic cell interactions within the niche comprising a number of soluble factors and cell-surface receptors; interestingly, some of these molecules, such as Wnt, Notch, transformation Growth Factor Receptor beta (TGF-b), bone morphogenetic proteins (BMPs) and others, are known to be involved in tumor development.

TARGETTING BREAST CANCER STEM CELLS

Cancer stem cells are slow-dividing and have a lowered ability to undergo apoptosis and a higher ability of DNA repair, making them more resistant to traditional methods of cancer treatment such as radiation and chemotherapy (Phillips T *et al*, 2006). In addition, stem cells express ABC drug transporters, which protect the cell from cytotoxic agents and reduce the efficacy of chemotherapeutic drugs (Dean M *et al*, 2005). However, in a single patient, tumours are heterogenous, with individual tumour cells displaying different phenotypes and Tumor Associated Antigens (TAAs).

This raises the possibility in immunotherapy that no single antigen can be used to effectively target and eliminate all tumour cells as there will likely be a resistant cell not expressing the targeted antigen that is capable of repopulating the tumor. Targeting of the BRCSC pool could potentially eliminate this population (Brian J Morrison *et al*, 2008). According to the above described characteristics of cancer stem cells, it is clear that available that most of the currently practiced anticancer therapies using more than 30 new anticancer drugs target the bulk of tumor cells debulking the tumor mass but often do not eliminate the cancer stem cells which causes tumor relapse and metastasis in the later phase (Gupta PB *et al*, 2011; Chaffer CL *et al*, 2011; Weir H *et al*, 2003)**.**

Therefore, to bring out effective therapy, debulking of differentiated tumours must occur followed by targeting of the remaining surviving, often quiescent, tumour stem cells. There are at least three potential ways to target breast CSCs: (1) inhibition of self-renewal signalling pathways thereby inducing differentiation or apoptosis, (2) targeting resistance

mechanisms and (3) targeting of the CSC niche (Matthew P A *et al*, 2012) (Fig 3).

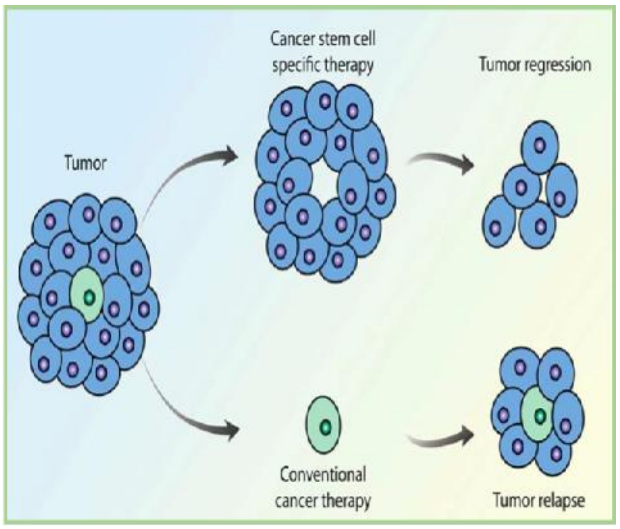

Figure 3 Targeting Cancer Cell and Cancer Stem Cell – A Model

In this model, in the first approach, cancer stem cell is targeted and thus shows a remarkable reduction in the size of the tumor whereas the second approach targets only cancerous cells in a tumor bulk which causes relapse in the later stage (Figure courtesy: Harvard Stem Cell Institute. http://hsci.harvard.edu/stem-cells-and-cancer)

Targeting Cancer Stem Cell Signaling Pathways

Notch pathway has been investigated as a target. Studies in pre invasive ductal carcinoma in situ and invasive breast cancer cell lines and clinical samples have shown that inhibition of the Notch signalling pathway using a c-secretase inhibitor, DAPT, significantly reduces CSC activity (Harrison H *et al*, 2010; Farnie G *et al*, 2007). A direct role for dysfunction of Wnt pathway in cancer was also established and hence tyrosine kinase inhibitors have been shown to downregulate β-catenin signaling (Zhou L *et al*, 2003). Many of the genes involved in hedgehog signaling are known oncogenes. Specific inhibitors of hedgehog signaling such as steroid-like molecule cyclopamine are developed and being used to inhibit the growth of mammary carcinoma cells which has showed promising results (Kubo M *et al*, 2004; Massard C *et al*, 2006). The combined use of ATP-Binding Cascade (ABC) transporter inhibitors and chemotherapy could also be used to increase the efficiency of chemotherapeutic drugs to kill cancer stem cells (Dean M *et al*, 2005). Thus, inhibition of regulatory pathways involved in self-renewal using specific inhibitors may confer improved clinical outcomes by targeting BRCSCs (Fig 4).

Targeting DNA Repair Mechanisms and Apoptotic Resistance

Another method to target CSCs is to induce them to differentiate, and thus lose their self-renewal potential. To achieve this, the CSCs must exit their quiescent state and become actively cycling in order to divide and differentiate. Rexinoids and retinoids, strong inducers of differentiation, are the current standard differentiation therapy for cancers and have been shown to promote differentiation of BRCSCs in vitro (Ginestier C *et al*, 2009). Compounds are aimed at disrupting DNA repair mechanisms using inhibitors of an enzyme poly ADP-ribose polymerase-1(PARP) responsible for DNA repairing (Tutt A *et al*, 2009; Calvert H *et al*, 2009). It has also been reported that targeting anti-apoptotic proteins may improve treatment of ER_ cancers (Monks NR *et al*, 2004).

Targeting the Niche and the Microenvironment

Stem cell niches are defined as locations in a tissue which specifically can support the existence of somatic stem cells. Niches allow the repopulation of the stem cell compartment from migrating stem cells or even from differentiated cells if the stem cell compartment is depleted (Kai T *et al*, 2003; Nishimura EK *et al*, 2002; Potten CS *et al*, 1990). Tumor therapy that depletes stem cells, but does not eradicate the stem cell niche, could lead to repopulation of the stem cell niche with additional cancer stem cells (Woodward WA *et al*, 2005). Identification of the properties of stem cell niches will be important for targeting BCSCs as it will be necessary to disrupt the inappropriate signalling that the stem cell niche may provide to achieve lasting clinical effects.

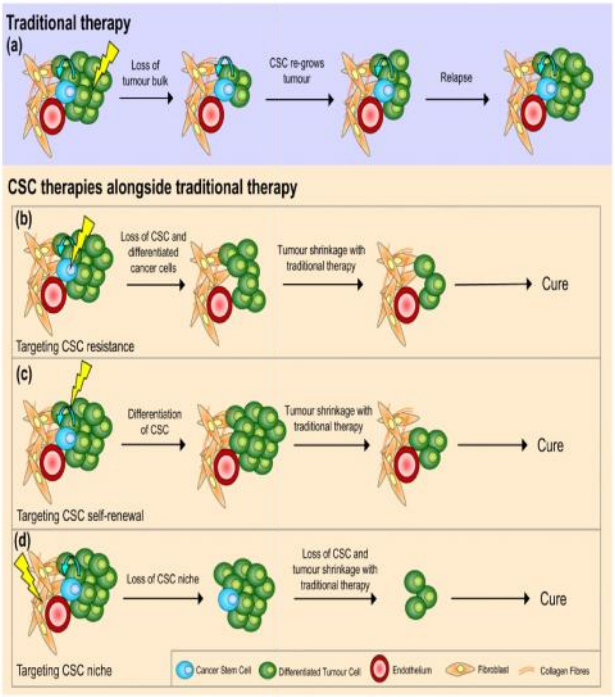

Fig 4 A CSC Model Depicting Novel Therapeutic Strategies

The possible effects of different cancer stem cell (CSC) therapies on tumour growth. Traditional therapy (a) targets the differentiated cells but does not affect all of the CSCs, leading to tumour relapse. Three strategies for CSC therapy are shown: (b) targeting CSC resistance, (c) targeting CSC self-renewal pathways or (d) targeting components of the CSC niche. Each of these strategies would be predicted to reduce the capacity for the CSCs to self-renew and repopulate the tumour. Use of these CSC therapies alongside traditional therapies should further reduce breast cancer recurrence rates. (Figure Courtesy Matthew *et al*, Eur J Cancer (2012), In Press, http://dx.doi.org/10.1016/j.ejca.2012.03.019)

Solid tumors are not simply a homogenous sheet of epithelial cells, such as in vitro culture rather tumors are composed of epithelial cells, fibroblasts, endothelial, hematopoietic, and other cells that communicate with each other in a complex network of growth factors and cytokines and the cognate receptors (Jin, L *et al*, 2006). The ability to interfere with this network is challenging. It is also well established that interactions among different cell types are responsible for correct tissue morphology and functionality. The clearest

evidence for this is provided by cell culture systems, where cells rapidly lose their distinguishing properties unless appropriate environmental requirements are satisfied. Thus, the microenvironment plays a key role in ruling cell positioning, proliferation and differentiation. There is a good deal of evidence that the microenvironment exerts a critical influence on tumour development and progression (Bissel MJ *et al*, 2005; Bhowmick NA *et al*, 2004). Integrins also mediate cell-extracellular matrix interactions and are key cell surface proteins used for enriching breast CSCs (Guan JL *et al*, 2010). Elevated levels of the intracellular signalling mediator, focal adhesion kinase (FAK), have been linked with increased invasion (Owens LV *et al*, 1995) [78]**.** Alterations affecting stromal cells have been shown to promote formation of epithelial tumours (Woodward WA *et al*, 2007; Atkinson RL *et al*, 2010)**,** and local modifications of tissue homeostasis induced by chronic inflammation may result in tumour development. Taken together, it is suggested that targeting CD44 or integrin related proteins associated with the CSC niche (e.g. FAK) may provide an alternative strategy in breast cancer therapy.

CONCLUSION

The concept of cancer stem cells has gained prominence in the recent years in terms of potential therapeutic targets and their impact on the treatment of the disease. Deciphering mammary cancer needs elucidation on normal mammary gland development, normal breast stem cells and progenitors, their self renewal and differentiation pathways, transformation of normal mammary stem cells in to breast cancer stem cells and their central role in tumorigenesis, cell surface markers for the identification of the breast cancer stem cell population, their niche and the microenvironment which has the ability to repopulate the cancer stem cells causing tumor relapse and metastasis.

Novel treatments need to be further developed as combination therapy with the existing treatments, which will allow targeting breast cancer stem cells after traditional radiotherapeutic, chemotherapeutic and immunotherapeutic treatments and destroy the remaining cancer stem cells. In addition to this, novel therapeutic strategies such as targeting cancer stem cell self renewal pathways, targeting cancer stem cell resistance or targeting components of the cancer stem cell niche might surpass the conventional therapy which targets only the differentiated cells but do not affect all of the cancer stem cells. This multimodal treatment regimen could be the most promising approach with significant clinical efficacy and improved quality of life for breast cancer patients.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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