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The Microenvironment of Breast Cancer Stem Cells

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1. Introduction

Ernst Haeckel first described the term "stem" as a concept for the evolution or organisms. For representation purpose he described the ancestor organism as a "stem" from which all the other organisms evolved. Arthur Pappenheim later adopted this concept in the context of cells, and he elegantly placed the "stem cell" in the centre in cartoon from which all the blood cells arise describing hematopoiesis (Ramalho-Santos and Willenbring, 2007).

The concept was carried forward and the term "cancer stem cell" was first coined in 1980 (Carney *et al.*, 1982) where the authors described the stem cell origin of lung cancer cells. The difficulty in isolation and the absence of specific markers of cancer stem cell stalled the research in this area. However a decade later Bonnet and Dick successfully isolated CSC in AML which then incited the development in the field of cancer stem cells (Bonnet and Dick, 1997). Their discovery was later supported by many groups, which also resulted in isolation of CSC from a variety of malignancies including solid tumors.

Now a large body of evidence suggests that cancer comprises of different population of cells with various tumorogenic potentials. The tumor cells follow a hierarchy, where the subset capable of self-renewal, generate the tumor heterogeneity and are called cancer stem cells (CSC). Very low number of these cancer stem cells generates tumors in immunocompromised mice whereas large number of non-CSCs fails to generate tumors.

CSCs have been characterized based on their ability to form colonies in soft agar and their ability to form spheres in serum free media. The generation of tumors in immunocompromised mice however remains the gold standard. Another characteristic of CSC is their ability to resist the action of common chemotherapeutic drugs which is attributed to higher expression of ABC transporters and their slow cycling nature. Further it has also been documented that these CSCs have activated signaling pathways as in the case of normal stem cells. Hence CSCs are distinct from other non-CSC in many respects.

Cancer stem cells have been isolated based on membrane markers. One of the characteristics is their ability to efflux the Hoechst dye. However this ability to efflux the dye is also attributed to membrane ABC transporter ABCG2. ABCG5 has been used as a cancer stem cell marker as it pumps out the drug doxorubicin. ALDH1 has the ability to convert retinol to retinoic acid, which has diverse role in cell physiology, and this activity is used as a marker for CSC. CD 44, CD 133, EpCAM and CD 90 are also abundantly expressed in CSCs and are used to isolate or enrich CSC (Visvader and Lindeman, 2008). A number of groups have isolated CSC based on these markers however a robust marker for CSC still remains to be identified.

1.1 Origin of CSC

A number of theories have been proposed for the generation of these CSCs. (1)CSC can originate from genetic/ epigenetic alteration of normal stem cells or from the progenitor cells. (2) They can be derived from somatic tumor cells by de differentiation or reprogramming into a stem- like cell (Visvader and Lindeman, 2008). (3) And recently it has been suggested that CSC can be generated from non-CSC through production secretary molecules (Iliopoulos *et al.*, 2011).

2. Breast cancer stem cells

The existence of cancer stem cells was first demonstrated in solid tumors by Al Hajj et al., where CSCs were identified from human breast cancer tissue using $CD44^+$ / $CD24^-$ Lin^- as cellular markers (Al-Hajj *et al.*, 2003). They isolated the cells from primary breast cancer or metastatic pleural effusions and injected them directly in to mice or after cellular sorting with the above mentioned markers. They found that $CD44^+$, $CD24^-$ were able to form tumors while $CD44^-$, $CD24^-$ were unable to form tumors in immunocompromised mice. Further they performed repopulation assays where they found that the tumorigenic population ($CD44^+$ / $CD24^-$ Lin^-) was able to give rise to phenotypic heterogeneity of the initial tumor. This suggested that the breast cancer stem cells undergo self-renewal and differentiation as in the case of normal stem cells. After this report a large number of studies identified CSC from various other malignancies (Curley *et al.*, 2009; Fang *et al.*, 2005; Kondo *et al.*, 2004; Liu *et al.*, 2007; Prince *et al.*, 2007; Singh *et al.*, 2004).

The normal stem cells reside in a distinct environment called the "stem cell niche". This stem cell niche consists of complex composition of ECM, soluble factors, stromal cells, immune cells which are responsible for maintaining the self renewal ability of stem cells. Similarly the CSCs also depend on similar environment, which may be altered in many ways. Moreover in some of the tumors, the tumor niche has been shown to have a protective role from genotoxic insults (Garcia-Barros *et al.*, 2003). Although much research has been done on understanding the cancer stem cells, very few studies have been carried out on understanding the microenvironment of breast cancer stem cells and their targeting. We believe that understanding the breast cancer microenvironment will offer easily tractable solutions to cancer therapy.

2.1 Role of microenviroment in mammary gland development

The breast tissue is composed of multiple cell types for proper functioning of tissue and the primary function of which is production of milk. During lactation milk is produced by the luminal epithelial cells and secreted in the hollow cavity. The luminal epithelial cells are surrounded by myoepithelial cells, which synthesize the basement membrane. Together the luminal epithelia and the myoepithelia form the milk duct. Different cell types whose function is to maintain the homeostasis surround milk duct. These cells include fibroblasts, leucocytes and endothelial cells.

The environment of epithelial cells plays a critical role in shaping their function. For eg. When the epithelial cells from breast tissue were placed on plastic, they were unable to produce milk and exhibited different phenotype as compared to the cells when plated in 3 dimentional reconstituted basement membrane (Matrigel) which led to proper function of epithelial cells (Howlett and Bissell, 1993; Petersen *et al.*, 1992). Hence proper cellular interaction and spatial localization of cells with the right constituents are required for

correct functioning of epithelial tissue. This was explained by the fact that invivo normal mammary gland are in contact with myoepithelial cells and not the basement membrane.
Further luminal epithelial cells display apical–basal polarity as demonstrated by MUC 1, ESA and occludin expression on the apical membrane and ß4 integrin on the basolateral membrane. However such a polarity is observed when luminal cells are grown in matrigel but not in collagen(Gudjonsson *et al.*, 2002). The polarity is restored when the myoepithelial cells are co- cultured with luminal epithelial cells even in collagen, which is mediated by laminin 1 secreted by myoepithelial cells. These studies demonstrate the role of 3D environment and is important for optimal function of epithelial cells.

2.1.1 Microenvironment of breast cancer cells

A large number of reports demonstrate that breast tumor progression is facilitated by stromal cells and that their presence is critical for survival of cancer cells. However it is also important to note that the normal mammary gland microenvironment has inhibitory effect on breast cancer progression (DeCosse *et al.*, 1973). This indicates that cancer cells can maintain their properties only in an abnormal microenvironment. One of the recent reports underlies the role of mesenchymal stem cells in amplifying the metastatic potential of weakly metastatic cells. Karnoub A et al mixed a weakly metastatic cell line MDA MB 231 with bone marrow derived human MSC and found that the metastatic potential of the cell line is dramatically increased (Karnoub *et al.*, 2007). To further understand the mechanism of this increase in metastatic potential they used a cytokine array to identify soluble factors. They found CCL5 release, which was induced by physical interaction between breast cancer cells and the MSC, and that it renders the breast cancer cells more metastatic.
Another seminal report by Kaplan et al demonstrate that bone marrow- derived hematopoietic progenitors may localize to future sites of metastasis and "prepare" the sites for the arrival and growth of disseminated cancer cells (Kaplan *et al.*, 2005). This has been proposed a new concept in metastasis, which is called the "premetastatic niche". The precise mechanism and the factors responsible for such localization of bone marrow derived hematopoietic progenitors is unclear however it appears to be derived from the serum (Kaplan *et al.*, 2005).
One of the extensive study in understanding the breast cancer microenvironment, Allinen et al. performed genome wide gene expression analysis of stromal cells (Endothelial cells, infiltrating leukocytes, fibroblasts, and myofibroblasts) and breast epithelial cells (luminal epithelial and myoepithelial cells) from normal, insitu carcinoma and invasive carcinoma. The authors found that alterations in gene expression takes place in all cell types however clonally selected genetic alterations are confined to tumor epithelial cells. Further there were consistent and significant alterations in myoepithelial cells from DCIS as compared to normal myoepithelial cells and many of these changes were in secreted proteins and cell surface receptors (Allinen *et al.*, 2004). This further underlines the importance of soluble factors in breast cancer progression.
Although a large amount of literature is present on microenvironment of breast cancer cells, there are few studies on cancer stem cell microenviroenment. This is ascribed to the age of this new field however research in this direction will significantly impact the therapy of breast cancer.

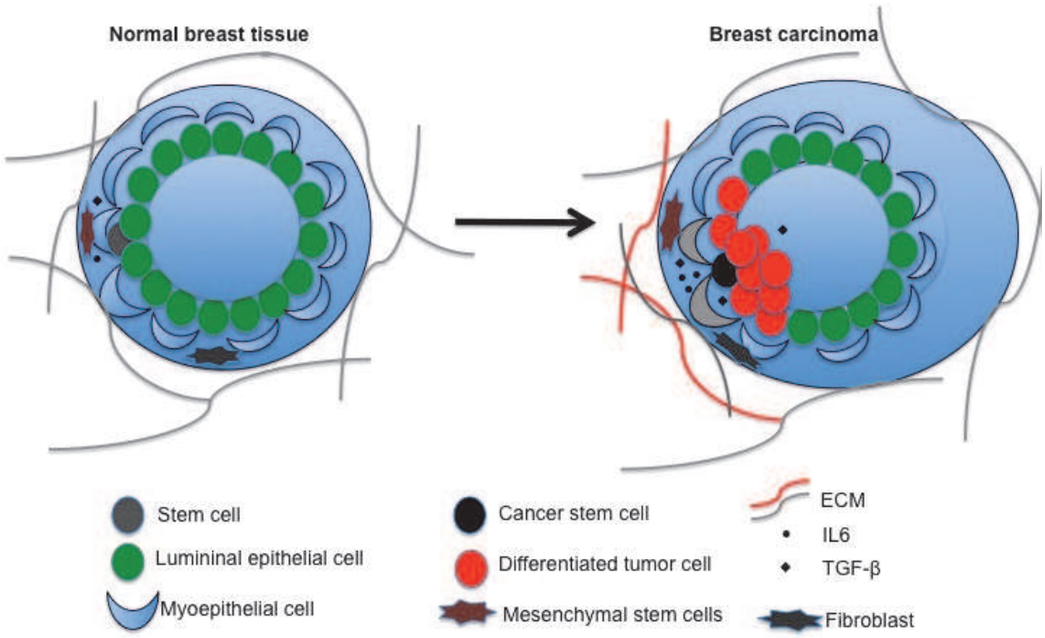


Fig. 1. Microenvironment of normal breast epithelium and breast cancer cells.

2.1.2 Influence of microenvironment on development of breast cancer stem cells

A limited number of factors have been studied to understand the interaction of microenvironment generated by tumors and its effect on development and maintenance of cancer stem cells. One of the widely studied environment which the solid tumors reside in, is hypoxia.

2.1.2.1 Hypoxia

It has been suggested that hypoxia contributes to the generation aggressive cancer by selecting tumor cells and results into growth of cells that can survive compromised levels of oxygen and nutrients (Graeber *et al.*, 1996). Further the growth of tumor results in hypoxic microenvironment, which is followed by periods of reoxygenation. Hence to mimic the invivo environment and to assess the fate of cells undergoing periods of hypoxia-reoxygenation Louie E etal., exposed breast cancer cells (MDA-MB-231 and BCM2) to cycles of hypoxia and nutrient deprivation. They discovered that after the first cycle of hypoxia a small fraction of cells survived and that repetitive exposure of the same cells to hypoxia and reoxygenation led to increased viability under hypoxia and to proliferate either as monolayer or tumor spheres. They also found increase in the number of cells expressing CD44+/CD24-/ESA+ cell surface markers, and hence the cancer stem cell content. Therefore repetitive cycling of hypoxia and re-oxygenation can increase the stem cell content of metastatic breast cancer cell lines indicating that microenvironment plays an important role in selectively increasing CSC (Louie *et al.*, 2010).

2.1.2.2 Stromal cells

Carcinoma associated fibroblasts (CAF)

For a long time scientist have primararily focused on epithelial component of breast cancer, however recently, the critical importance of tumor stroma has been realized. Literature

documents important interaction between mammary epithelia and the adjacent tumor stroma. One of the reports demonstrates that CAF increases the number of $CD44^{+}CD24^{-}$ cells in mammospheres, whereas normal fibroblasts (NFs) down-regulated it in mammospheres. They also demonstrate increase in the ability to form epithelial tumors in immunocompromised mice in presence of CAF. This indicates that CAFs can increase the cancer stem cell population in breast cancer (Huang *et al.*, 2010). Furthermore since, CXCR4 expression on carcinoma cells is known to correlate with a poor prognosis for several types of carcinomas (Balkwill, 2004), the authors assessed CXCR4 gene expression in mamosphere co cultured with CAF. They found increase expression of CXCR4 and it was speculated that increase in cancer stem cell population could be because of CXCR4 signaling (Huang *et al.*, 2010).

The normal fibroblasts on the contarary have a inhibitory effect on the tumor growth. For e.g Coculture studies using different mesenchymal cells and MCF10A and preneoplastic MCF10AT1-EIII8 mammary epithelial cells showed that fibroblasts derived from normal reduction mammoplasty inhibit or retard the morphological conversion and growth of MCF10A and EIII8 cells, whereas tumor derived fibroblasts evoke ductal-alveolar morphogenesis of both cell types (Shekhar *et al.*, 2001). Further caveolin-1 deficient (Cav1-/-) mammary stromal fibroblasts were shown to mimic the effects of human breast cancer associated fibroblasts as they show similar profile of RB/ E2F-regulated genes that are up-regulated and confer a poor prognosis with enhanced epithelial-mesenchymal transition (EMT) (Sotgia *et al.*, 2009).

Interestingly, genome-wide expression profiling of human breast cancer-associated fibroblasts and Cav-1 (-/-) mammary stromal fibroblasts indicates that they both show the upregulation of a number of ES-cell related genes and factors (Oct4, Nanog, Sox2 and Myc-target genes), indicating that they may behave like "cancer stem cells". Thus, the tumor stromal microenvironment may directly contribute to maintaining the "cancer stem cell" phenotype, leading to drug-resistance and treatment failure (Sotgia *et al.*, 2009).

Fibroblast synthesize growth and survival factors which are critical for the tumor. In breast cancer, stromal fibroblasts evolve with the tumor epithelial cells and assist the growth of tumor cells. Inspite of much known about role of stromal cells the mechanistic basis of such a requirement of fibroblast remains elusive. PTEN is a tumor suppressor and is a critical regulator of PI3K signaling whose activation is associated with activation of tumor stroma (Cully *et al.*, 2006). To understand the role of fibroblast in tumor formation Trimboli et al deleted PTEN from fibroblast in MMTV- ERBB2 mice model. They found that deletion of PTEN from fibroblast results in increase incidence and tumor load in the mice model. Extensive remodeling of ECM and increased recruitment of innate immune cells were some of the salient findings. Gene expression analysis revealed that PTEN deleted stromal fibroblasts consists of activation of Ets2 transcription factor. Further double transgenic mice having inactivation of Ets2 in mammary stroma reversed the increased malignancy caused by PTEN deficiency. These observations show the importance of the PTEN-Ets2 axis in stromal fibroblasts in the *MMTV-ErbB2* model in suppressing breast cancer growth and indicate the stromal pathway contributes to the complexity of human breast cancer stroma (Trimboli *et al.*, 2009).

Mesenchymal stem cells

Mesenchymal stem cells localize to the breast carcinoma and integrate into tumor associated stroma. A seminal report by Ling X et al., demonstrate that MSC overexpressing IFN-beta inhibit breast cancer growth and metastasis (Ling *et al.*, 2010). They demonstrate that MSC

are recruited to tumors and that IFN-beta inhibits tumor growth. (Ling X 2010). Such a reduction in tumor could also be attributable to decrease CSC content. Karnoub A et al., have shown increase in the metastatic potential of the breast cancer cells when they were mixed with bone marrow derived human MSC. Using a cytokine array they identified CCL5 is induced by physical interaction between breast cancer cells and the MSC, and that it renders the breast cancer cells more metastatic. These results indicate the importance of mesenchymal stem cells in rendering the cells more metastatic (Karnoub *et al.*, 2007).

2.1.2.3 Stromal factors

IL-6

IT has been documented that CSCs arise from mutant versions of normal stem cells. Alternatively, CSCs can also represent a stage in the path of transformation. CSCs are precursors of differentiated cancer cells (NSCCs), however CSCs can also be derived from NSCCs or can arise independently. The proportion of CSCs remains constant over multiple generations, but the basis of this phenomenon is unknown. Hence Iliopoulos D et al., assessed these issues using an inducible model of oncogenesis that MCF-10A cells which harbor a ligand-binding domain of estrogen receptor (ER-Src), a derivative of the Src kinase oncoprotein (v-Src) that is fused to the ligand-binding domain of the estrogen receptor. Treatment of these cells with tamoxifen (TAM) rapidly induces Src, results in transformation within 24-26 h. This property of the model helps in understanding the transition between normal and transformed cells. The authors then discovered that induction of CSC from non-CSC through activation of v-src. They also document that CSC formation depends on transformation however it is not required for transformation. Moreover because of the fact that breast CSCs have an enhanced inflammatory feedback loop compared with NSCCs, they treated the cells with IL6 which resulted in generation of CSC fron non-CSC (Iliopoulos *et al.*, 2011). This indicates the critical role of microenvironment as the CSC itself secrete IL6 which can maintain the stemness of a cancer cell population. Further the fact that macrophages and dendritic cells are potent IL-6 producers, which can be activated by molecular "danger" signals by cancer cells it is important to control the IL6 signaling to regenerate the CSC .

TGF beta

One of the elegant studies by Mani et al demonstrates the role of TGF beta in cancer stem cell through induction of EMT. The authors treated the immortalized HMEC cells with TGF beta which resulted in fibroblast like, mesenchymal like phenotype with concomitant downregulation of ephtielial markers like E-cadherin and upregulation of mesenchymal markers like vimentin, fibronectin and N-cadherin. Similar results were obtained through ectopic expression of TWIST or SNAI1. They further assessed the CD44 and CD24 population of these cells and found that CD44+ and CD24 ^{low} cells were increased which TGF beta treatment/ TWIST, SNAI1 expression. The rise in CD44+ and CD24 low population was accompanied by approximately 30-40 fold enrichment in mamosphere forming capability (Mani *et al.*, 2008). This was a clear demonstration of TGF beta induction of cancer stem cell population.

Yin X et al., showed that the activating transcription factor 3 (ATF3) is induced by TGF beta in breast cancer and is important for increasing the migration potential of the breast cancer cells. Further ATF3 can be induced by a number of stromal factors like TGF beta, IFN alpha, TNF alpha and hypoxia. And the fact that ectopic expression of ATF3 increases the cancer stem cell content of breast cancer cells (CD 24^{low}/ CD 44^{high}), it was hypothesized that tumor microenvironment has a significant effect in the development of cancer (Yin *et al.*, 2010).

2.1.2.4 Embryonic microenvironment

Four decades back it was documented that embryonic microenvironment can reprogram the cancer cells to a benign phenotype; however, the mechanisms underlying this phenomenon remains unclear (Hendrix *et al.*, 2007). The human embryonic stem cells (hESC) and cancer cells have various common features however hESC do not form tumors owing to the ability to differentiate in response to signals from the microenvironment. Normally the stem cell microenvironment or the stem cell niche controls the fate of the stem cells and that it provides the necessary constituents for maintaining homeostasis of tissue (Fuchs *et al.*, 2004). In cancer cells such control is lost and that restoring the niche may result in maintaining the homeostasis of growth and normal differentiation.

Hence to understand the mechanism Lynne-Marie Postovit et al (2006) developed an in vitro 3D model to investigate the capacity of hESC-derived factors to epigenetically influence metastatic cancer cells. They showed exposure of melanoma cells to a hESC microenvironment results in the reexpression of melanocyte-specific markers which are indicative of differentiation and a reduction in invasive potential.

Further (Lynne-Marie Postovit, 2006) they discovered that hESC microenvironments suppress the tumorigenic phenotype of human metastatic melanoma and breast carcinoma cells and that this effect is is brought about only by hESCs and not other stem cell types. Further they found that hESC microenvironment neutralize the aberrant expression of Nodal in metastatic melanoma and breast carcinoma cells and reprogram them to a less aggressive phenotype (Postovit *et al.*, 2006a; b). They also identified lefty which is sectreted by hESC (an inhibitor of Nodal signaling) as an important mediator of these phenomena. Hence the microenvironment of hESCs provides a previously unexplored therapeutic entity for the regulation of aberrantly expressed embryonic factor(s) in aggressive tumor cells (Postovit *et al.*, 2008).

3. Conclusion

CSC are rare cells and they are distinct from other bulk tumor cells. They generate the tumor and maintain the tumor hetrogenity. If the CSCs are elemiminated/differentiated to nonCSCs then cancer can be eradicated. The CSC niche maintains the CSC characteristics and increases the CSC potential, hence CSC niche offers a critical window treatment of cancer. Hence strategies that target the pathways critical for selfrenewal which are maintained through niche should be the focus of therapy. Notch, Wnt and Hedgehog pathways are known for maintaining self renewal of normal stem cells (Merchant and Matsui, 2010; Pannuti *et al.*, 2010; Takahashi-Yanaga and Kahn, 2010). These pathways offers targets in combination of other tumor specific markers for CSC targeting. For eg. Farnie, G et al., demonstrated that inhibiting notch signaling using gama secretase inhibitors in DCIS derived cells decreases their mamosphere forming efficiency (Farnie *et al.*, 2007). Further antibodies against the ECM Protein fibronectin receptor α4β1 integrin prevented the interaction of cancer cells with premetastatic niches and reduce the minimal residual disease (Kaplan *et al.*, 2005). Moreover antibodies to fibronectin and β1 integrin promoted epithelial phenotype of invasive breast cancer cells in organotypic three dimentional cultures (Sandal *et al.*, 2007). Hence when formulating such therapeutic modalities a combination of inhibitors/biomolecules which can efficiently inhibit the cancer stem cells self renewal should be considered.

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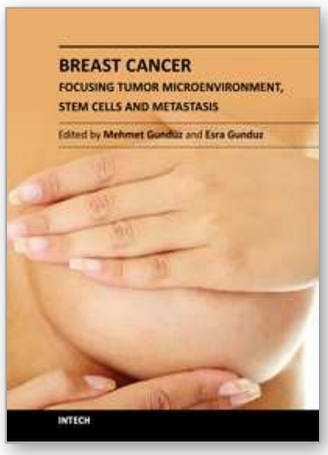
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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed characteristics of breast cancer cell, role of microenvironment, stem cells and metastasis 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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