Journal of Molecular Biomarkers & Diagnosis
ISSN: 2155-9929

van Golen and van Golen, J Mol Biomarkers Diagn 2012, S:8
DOI: 10.4172/2155-9929.S8-002

Review Article Open Access

Inflammatory Breast Cancer Stem Cells: Contributors to Aggressiveness, Metastatic Spread and Dormancy

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Abstract

Cancer stem cell populations have been identified for several types of cancers and suggest a way for tumor cells to be resistant to therapies. Further, because of the longevity, endurance and replicative potential of cancer cells with stem-like properties, other malignant attributes such as recurrence after long periods of dormancy can also be explained. Inflammatory breast cancer (IBC) is a unique and aggressive form of breast cancer that has a clinical course unlike other forms of breast cancer. The main hallmark of IBC is prolific invasion of the dermal lymphatic vessels by tumor emboli leading to rapid metastasis of the disease. Despite an extremely aggressive treatment approach, the majority of women with IBC present with disease recurrence suggesting the presence of chemo resistant and/or dormant breast cancer cells. Current evidence suggests that IBC tumor emboli contain distinct populations of cells with stem cell-like properties. Thus, specific targeting of these stem cell-like cancer cells may be the key to effectively treating IBC.

Keywords: Inflammatory breast cancer; Breast cancer stem cells; Dormancy; Metastasis

Introduction to Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is arguably the most aggressive and persistent form of breast cancer known with 5- and 10-year disease-free survival rates of <42% and <20%, respectively [1-4]. IBC is extremely unique in its manifestation, presentation and molecular pathology [5-7]. This form of breast cancer affects younger women with a mean age of ~ 46 years old and is reported in girls as young as 12 years old [8-10].

The term inflammatory breast cancer was first coined by Drs. Lee and Tannenbaum in 1924 to unite what was thought to be a number of individual cancers that affected younger women, under a single term [11]. However, the term "inflammatory" breast cancer is a misnomer, as the tumor lacks the conspicuous presence of immune effector cells [8,12]. The appearance of the disease does resemble that of an infection with a number of primary skin changes that occur including redness, thickening of the skin, erythema, peau d' orange and warmth to the touch [7,8,11,12]. In addition, the breast size increases and can be sore, the nipple can invert and if advanced, the breast can become necrotic [7,8,11,12]. Patients report that the onset of these symptoms can occur within a very short period of time 24-48 hours.

A palpable mass is often missing in IBC. Instead the primary tumor presents as diffuse cords or sheets in the breast [7,8,11,12]. IBC is highly lymph invasive and the main hallmark of the disease is lympho vascular invasion of the dermal lymphatic vessels of the skin overlying the breast [7,13,14]. It is suggested that the presence of the tumor emboli within the dermal lymphatic vessels cause edema and the skin changes described above. However, physicians report a persistence of symptoms after treatment and apparent complete pathological response [15]. Unfortunately, due to the nature of these symptoms coupled with the rapidity of onset, IBC is often misdiagnosed as an infection and inappropriately treated [15,16]. IBC experts estimate that nearly 90% of IBC cases are initially misdiagnosed.

It is also suggested that the presence of tumor emboli in the dermal lymphatic vessels are responsible for the prolific metastasis associated with IBC. By definition, IBC is a T4d tumor and is always diagnosed as a stage IIIb or IV tumor, with all women having lymph node involvement and nearly 1/3 having gross distant metastases in visceral organ, bone and brain [2,7,8,17]. The progression to advanced disease is extremely rapid, progressing from what appears to be normal breast to advanced disease within 6 months [7].

As stated above, IBC is molecularly distinct from other forms of breast cancer [5]. Our laboratory was the first to identify genes uniquely altered in IBC, particularly RhoC GTPase, which is over expressed in over 90% of IBC patient specimens [19]. We demonstrated that active RhoC GTPase is required to drive the invasive IBC phenotype through reorganization of the actin cytoskeleton [20,21]. Extensive analysis has shown that IBC expresses a unique gene profile compared to cell-type of origin matched, stage matched or receptor status (eg. estrogen receptor/progesterone receptor (ER/PR) +, Her2+ or triple negative) non-IBCs [14,22]. Interestingly, many gene changes that are observed during progression of non-IBC are opposite for IBC [5,6]. For example, E-cadherin and caveolin-1 and -2 are over expressed in IBC compared to non-IBC [13,26,27].

In addition to the unique molecular signature and route of dissemination, IBC tends to be resistant to therapy [3,28]. Recurrences, including chest wall recurrences, are common and often occur in soft tissue and visceral organ [29]. Because of this, many people believe that IBC emboli contain a large number of breast cancer cells with stem cell-like properties. The SUM149 IBC cell line, emboli from the Mary-X

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Received May 21, 2012; **Accepted** June 20, 2012; **Published** June 25, 2012

Citation: van Golen CM, van Golen KL (2012) Inflammatory Breast Cancer Stem Cells: Contributors to Aggressiveness, Metastatic Spread and Dormancy. J Mol Biomarkers Diagn S8:002. doi:10.4172/2155-9929.S8-002

xenograft model and IBC patient emboli are shown to contain a large population of cancer cells with a stem cell signature [30,31].

Cancer Stem Cells in Inflammatory Breast Cancer

Cancer stem cells became a wide spread interest with the identification of putative stem cells in leukemia [32]. Since that time, cancer stem cells have been identified for multiple hematologic and solid tumors, including breast, prostate, brain, skin, liver, and lung tumors [33]. As with all stem cells, tumor stem cells have prolonged self-renewal capacity and the potential to produce progeny that will differentiate into specialized cells of the tissue of origin [34]. The original determination of a cancer stem cell population was based upon the ability of those cells to reform a tumor *in vivo*, usually experimentally determined through serial injection into immune compromised experimentally [34,35]. Based upon these criterion, tumor stem cells are also known as tumor-initiating cells [33]. However, cancer stem cells are also closely linked to more advanced tumor phenotypes, including angiogenesis, chemo resistance, and metastases [33,36,37].

Several markers have been identified in cancer stem cells, including those from breast carcinoma. CD44 is considered a stem cell marker for several tumors, including bladder, breast, colon, and head and neck. CD133 is another common marker, found in stem cells from colon carcinoma, Ewing's sarcoma, and pancreatic cancer. In breast carcinomas, the absence of CD24 is also indicative of a stem cell phenotype [34,38]. In addition to these markers, signal transduction pathways involved in the breast cancer stem cell phenotype have been elucidated. Notch signaling, involved in differentiation and cell fate determination during development, is up-regulated in breast cancer stem cells and correlates with the CD44+/CD24- marker phenotype [39]. Furthermore, inhibition of Notch signaling abrogates cancer stem cell self-renewal [39]. Tumor necrosis factor alpha (TNF), acting through the nuclear factor kappa B (NF-κB) signaling pathway, up-regulates SLUG, a mediator of the epithelial to mesenchymal transition in breast cancer cells. SLUG up-regulation in turn promotes a stem cell phenotype within breast cancer cells [40]. Additional pathways implicated in the breast cancer stem cell phenotype include those of aldehyde dehydrogenase [41], bone morphogenic protein (BMP), Wnt [42] and ganglioside GD2 [43].

As previously discussed, IBCs are highly aggressive and metastatic at diagnosis. Given the aggressive nature of this tumor, it is not surprising that experimental evidence supports the involvement of breast cancer stem cells in its progression. Tumor cells isolated from the MARY-X model of human IBC express both embryonal stem cell markers (Nestin, Rex1, and Stellar) and the classic breast cancer stem cell signature (CD44+/CD24-/CD133+/aldehyde dehydrogenase1 (ALDH1)+) [31]. Furthermore, 74% of human IBC samples contain a genetic signature indicative of a high cancer stem cell composition, as opposed to 44% of non-IBC samples [42]. Stem cell-related signaling, particularly through Hedgehog and transforming growth factor beta (TGF**β**), is also more active in IBC vs. non-IBC samples [42]. Nestin, a protein primarily associated with neural stem cells, is highly expressed in both triple negative and IBC tumors [44]. As with other types of breast tumors, ALDH1 is highly up-regulated in IBC, and its expression correlates with increased metastasis and decreased survival [30]. Finally, IBCs express a unique microRNA (miRNA) profile, and several of these miRNAs are also expressed in tumor stem cells [45]. Therefore, the presence of high stem cell content in IBC may contribute to the aggressive nature of this disease, but may also offer attractive therapeutic targets.

Farnesyl Transferase Inhibitors as Potential Cancer Stem Cell-Targeted IBC Therapeutics

Farnesyl transferase inhibitors (FTIs) were originally developed to target Ras-based tumors [46]. However, their performance in the clinic was disappointing thus, attention turned to non-Ras targets, specifically Rho GTPases [47,48]. In a study of the effects of FTIs on the SUM149 IBC cell line, we observed a significant, but reversible, loss of RhoC GTPase-mediated motility and invasion [49]. These results strongly suggest that FTIs could be used as novel adjuvant therapy for IBC [49].

Interestingly, FTI-treated IBC cells exhibited a unique spread and flattened morphology with pronounced actin stress fibers [49]. This unique morphology is reminiscent of what is described for an *in vitro* model of breast cancer cell dormancy [51]. Interestingly in this model, RhoA GTPase activity was decreased [52,53]. RhoA and RhoC GTPases tended to have opposing actions in tumor cells, exhibiting a balance between inactive and active forms of the two GTPases [54,55].

The mechanisms of tumor cell dormancy are currently not well understood. In a recent study from our laboratory we demonstrated that treatment of MCF-7 non-IBC cells with FTI L-422,831, leads to a phenotype reminiscent of dormancy [56,57]. Further, FTI treatment of the MCF-7 cell line leads to profound changes in Rho GTPase activation [56,57]. Specifically, RhoA GTPase becomes hypoactivated while RhoC GTPase becomes hyperactivated, producing radical changes in the cell cytoskeleton and cellular morphology identical to what was observed in the FTI-treated SUM149 IBC cells [49].

Similar to what is observed for the *in vitro* model [51,52], FTI-induced dormancy is reversible [49,56,58]. Upon FTI withdrawal cells grow normally after exiting from nearly two weeks of dormancy [56]. FTI-treated cells have minimal metabolic activity and undergo autophagy [56]. Autophagy is the process where a cell degrades organelles such as mitochondria to expend less energy avoiding apoptosis [59]. Autophagy is regulated through the extracellular matrix and is suggested to be required for dormancy [60-62]. In addition, activation of the c-jun NH2 terminal kinase (JNK/SAPK) signaling pathway occurs during autophagy [63,64]. Increased RhoC GTPase activation during FTI treatment increases JNK/SAPK signaling leading to breast tumor cell dormancy [56].

Stem cell associated markers such as ALDH1 and CD44 are shown to be expressed by a subpopulation of cancer cells in both tumors and cells lines [65-67]. It is suggested that breast cancer cells with stem cell-like properties are responsible for metastatic spread [68,69], while RhoC GTPase is expressed by highly metastatic cancer cells that exhibit "stemness" properties [30,70]. Cancer stem cells have also been linked to dormancy. It is thought that a metastatic stem cell, arriving in a non-conducive microenvironment undergo prolonged dormancy until an event such as a cytokine storm or extracellular matrix remodeling re-activate cancer cells [68]. Breast cancer cells undergoing post-FTI-treatment dormancy, express ALDH1 and CD44, suggesting that breast cancer stem cells are susceptible to FTI-induced dormancy [57]. This phenotype is due to the activation of JNK/SAPK signaling resulting from increased RhoC activation. The activation of JNK/SAPK signaling in turn may lead to induction of autophagy allowing the breast cancer cells to remain inactive. These studies may have profound implications for the use of FTIs in the clinic. Potentially, FTI-induced dormancy could synchronize tumor cells; with FTI withdrawal would allow growth making the cells more susceptible to chemotherapeutics.

Conclusions

The presence of cancer stem cells in epithelial tumors, including IBCs, is now widely accepted, and laboratories are now therapeutically targeting several of the proteins associated with stem cell phenotypes. Breast cancer stem cells are highly resistant to traditional radio- and chemotherapy. ALDH1 can metabolize chemotherapeutic drugs, and CD44+/CD24- cells are enriched in remaining breast tumor tissue following chemotherapy [71]. Targeting HER2, a receptor thought to aid in the stem cell phenotype, may decrease this particular population of cells [69,70]. Small hairpin (sh) RNA targeting CD44 induces breast cancer stem cells to differentiate, resulting in a lower tumorigenic potential [70]. This putatively could reintroduce chemo-susceptibility in these breast cancer cells. In melanoma, antibodies targeting CD20 are effective at reducing the stem cell population and causing metastases to regress [71]. Therefore, antibodies or specific inhibitory agents targeting CD44, ALDH1, or other stem cell-like markers in IBC could be beneficial at reducing the aggressive progression of this disease.

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This article was originally published in a special issue, **Potential Biomarkers and Therapeutic Targets in Cancer Stem Cells** handled by Editor(s). Dr. Murielle Mimeault, University of Nebraska Medical Center, USA