International Journal of Biomedical Science and Engineering
2014; 2(6-1): 20-24
Published online January 27, 2015 (http://www.sciencepublishinggroup.com/j/ijbse)
doi: 10.11648/j.ijbse.s.2014020601.13
ISSN: 2376-7227 (Print); ISSN: 2376-7235 (Online)

Mesenchymal stem cell therapy for breast cancer: Challenges remaining

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To cite this article:

Armel Herve Nwabo Kamdje, Paul Faustin Seke Etet, Kiven Erique Lukong. Mesenchymal Stem Cell Therapy for Breast Cancer: Challenges Remaining. *International Journal of Biomedical Science and Engineering.* Special Issue: Cancer Research. Vol. 2, No. 6-1, 2014, pp. 20-24. doi: 10.11648/j.ijbse.s.2014020601.13

Abstract: The treatment of breast cancer, the most common malignancy among women worldwide, remains puzzling partly due to the resistance to therapeutics, which associates with the heterogeneity of case clinical presentations, and limits in the current understanding of the pathogenesis of solid cancers. Notably, it remains unclear: (*i*) whether breast cancer starts strictly as a local disease before metastasizing to the lymph nodes and distant organs, i.e. if cancer initiating cells are local cells that have undergone epithelial to mesenchymal transition; (*ii*) or if breast cancer is intrinsically a systemic disease started by malfunctioning circulating mesenchymal stem cells (MSCs) infiltrating the breast stroma to start tumorigenesis. Such limits in our understanding of breast cancer biology have been slowing the development of MSC-based therapies exploiting the ability of these cells to home into tumorigenic sites, kill cancer cells, stop neoangiogenesis, and repair damaged tissues, as well as therapeutic approaches using these cells as vehicle for gene therapy and for delivering anticancer therapeutics, which are potential game changing therapeutic approaches, particularly in currently incurable cancers and intractable cases. Major drawbacks to MSC-based therapy implementation and use in breast cancer are herein briefly discussed.

Keywords: Stem Cells, Breast Cancer, Microenvironment, Signaling Pathways, Therapy, Therapeutic Resistance

1. Background

Breast cancer remains the most common malignancy among women worldwide, despite efforts of medical and scientific communities, partly due to difficulties to convert experimental findings into clinically useful information. The incidence of this malignancy has been increasing, and the number of new cases is expected to double by the year 2020, reaching 20 million approximately, with the annual mortality rising from about 6.6 million currently to more than 10 million [1-3], if more efficient early detection strategies are not implemented and better therapeutic approaches introduced.

Herein, we will briefly summarize and discuss the huge body of recent evidence supporting a tremendous potential for stem cell therapy in breast cancer.

2. Mesenchymal Stem Cells and Cancer

MSCs are multipotent stromal progenitor cells mostly found in the bone marrow, which can differentiate in most cell types of mesodermal cell lineages (but also some non-mesodermal cells), including osteocytes, adipocytes, epithelial cells, myocytes, chondrocytes, neurons, fibroblasts, and myofibroblasts, among others [4, 5]. Interest for MSCs in solid cancer therapy rose from their ability to: (*i*) to home to sites of tumorigenesis, providing a mean for efficient delivery of anticancer drugs [6-9]; (*ii*) to suppress local inflammation [10, 11], which bears a potential for suppressing tumor-promoting inflammation, a hallmark of primary tumor microenvironment [12, 13] and relapse [14, 15]; and (*iii*) to promote damaged tissue repair and regeneration [16-18], without any immunogenicity and toxicity to the host.

MSCs represent a promising platform for cell and gene therapy of incurable cancers [13, 19, 20]. The high tropism of

MSCs to cancers, as well as their ability to engraft, survive, and proliferate in the tumor, makes them ideal vehicle for tumor-selective drug delivery. MSCs migrate to sites of tumorigenesis and have been utilized as efficient cellular vehicle for the targeted delivery of anti-neoplastic therapeutics to both primary tumors and their metastases [21]. Several preclinical studies support the basis for genetically modified MSCs to deliver therapeutics to tumor sites; include in glioma, melanoma, Kaposi's sarcoma, Ewing sarcoma, as well as carcinomas of the colon, ovary, and breast [21-28]. Unfortunately, mechanistic insights in MSC homing to sites of malignant growth are missing.

3. Recent Evidence for MSC Anticancer Role

Numerous reports support a therapeutic potential for MSCs in breast cancer. For instance, adipose tissue-derived MSCs cultured at high density suppressed the growth of MCF-7 human breast cancer cells via an IFN-β-dependent mechanism [29]. Similarly, in a co-culture study of human breast cancer cells and bone marrow-derived MSCs an inhibition of growth of breast cancer cells was observed [30]. Mechanisms explaining such effect included silencing of the oncogenic signaling mediated by truncated neurokinin receptor-1 (NK1R-Tr), the tumorigenesis and metastasis promoting factor SDF-1α, as well as TGF-β genes. Adipose tissue-derived MSCs also increased chemosensitivity of human breast cancer cells in co-culture [31].

Furthermore, a recent bioluminescence imaging study on a breast cancer xenograft mouse model [using human breast cancer cell line MDA-MB-231 carrying a reporter system encoding a double fusion reporter gene consisting of firefly luciferase (Fluc) and enhanced green fluorescent protein (eGFP)] treated with human umbilical cord-derived MSCs [armed with a triple fusion gene containing the herpes simplex virus truncated thymidine kinase (HSV-ttk), renilla luciferase (Rluc) and red fluorescent protein (RFP)] revealed that MSCs can induce apoptosis in breast cancer cells and suppress angiogenesis. [32]. In an in vivo preclinical model of mammary tumors induced by N-nitroso-N-methylurea (NMU), placenta-derived MSCs migrated towards mammary tumors both in vitro and in vivo, and reduced tumor growth and tumor development [33].

4. MSCs and Cancer Stem Cells

MSCs but also various other stem cell types, such as stem cells isolated from the normal mouse mammary gland and human breast reduction tissues [34], are able to perform epithelial-mesenchymal transition (EMT), a latent embryonic program whose aberrant activation would play a pivotal role in the development of chemoresistant cancer stem cells that support highly aggressive primary breast tumors [31, 35-37] metastases [38, 39]. And relapse [40, 41]. This raises concerns for a potential implication of MSCs in breast cancer pathogenesis, particularly in the current context where the origin of cancer stem cells remains elusive. Thus, though numerous reports suggest that cancer stem cells derive from epithelial cells that have undergone mesenchymal transition [42-46], there is also evidence that these malignant cells may derive from an expansion of pre-existing stem cell populations expressing EMT-associated markers, including MSCs [34, 47, 48].

Oncogenic signaling pathways, such as Wnt, Hedgehog (Hh) and Notch play important roles in cell proliferation regulations and contribute to the self-renewal of stem cells and/or progenitor cells [49-56] are highly expressed in tumor microenvironment [13, 57], where they play a pivotal role in EMT. These signaling pathways would also confer stemness and chemoresistance to a number of transforming cells, which would then become cancer stem cells (for review see [58-61]). Monoclonal antibody-based therapies targeting these cells have been proposed in order to improve the outcome of anticancer therapy, including targeting cancer stem cell specific markers and/or the oncogenic signaling pathways allowing their maintenance, survival, and proliferation [62].

5. Controversy on Stem Cell Biology and Cancer

A recent in vitro study using breast cancer clinical isolates reported that MSCs provide support to actively dividing cancer cells, and the secretome of MSCs isolated from various tissues included numerous cytokines and chemokines implicated in tumor growth and/or metastasis, such as CCL2, CCL5, IL-6, TGFβ, and VEGF [31, 63-66]. Such response of breast cancer cells to MSCs could even be increased by inflammation-associated with breast implants [67]. These observations are in agreement with current stem cell biology understanding, from which it can be anticipated as well that MSCs may also fuel breast tumorigenesis in vivo, if introduced massively to neoplastic sites [68-71]. In addition, cells of rare fibroepithelial breast tumors like malignant breast phyllodes were reported various characteristics of MSCs [72], as well as the ability to transform into rhabdomyosarcoma, liposarcoma and osteosarcoma, raising more concern about the use of MSCs in breast cancer.

Interestingly, a xenograft study using a combination of molecular imaging technologies, showed that it is possible to monitor the therapeutic effects, as well as basic molecular and cellular processes of MSCs in real time, but also to better guide MSC mediated cancer therapy, notably using combination therapies with classical chemotherapy drugs [32]. This approach represents a good strategy for preventing potential tumorigenic MSC activities in anticancer therapeutic approaches using these cells. The necessity of monitoring and guiding MSC mediated cancer therapy emerged from another imaging study (using fluorescence), where MSCs promoted mammary tumorigenesis by generation of a cancer-enhancing microenvironment [73],

and various in vitro studies with comparable results, including those discussed in the precedent paragraph. Another strategy for preventing MSCs carcinogenic effect emerged from a report suggesting that TGF-β signaling targeting in MSCs abolishes their pro-tumor effects, partly by preventing their transformation in highly pathogenic carcinoma-associated fibroblasts (CAFs), without affecting their stemness and other positive properties, including their tumor-tropic property [74]. Preactivation of human MSCs with TNF-α was also reported as a strategy for biasing MSCs towards tumor-suppressive profile [75]. In this study, weekly infusions into mice of TNF-α preactivated MSCs decreased the progression of lung tumors formed from MDA-MB-231 breast cancer cells.

6. Concluding Remarks and Perspectives

Breast cancer treatment is currently puzzling due to chemoresistance, particularly in some subtypes (like triple negative cancers) and in advanced (metastatic) stages. MSCs bear a high potential in breast cancer therapy, as they constitute a good vehicle for specific delivery of anticancer therapeutics to tumor sites and have tissue repair abilities. Corroborating the huge body of early experimental evidence, emerging clinical evidence also suggests that the use of MSC therapy in breast cancer could be a game changing therapeutic approach. However, it is unclear whether cancer stem cell originate from MSCs. In this case, MSCs may play a pivotal role in cancer tumorigenesis, and thus, strategies increasing their infiltration to breast would fuel tumorigenic processes. Future studies investigating the roles of MSCs in breast tumorigenesis and metastasis formation are necessary, considering the potential of MSCs for breast cancer treatment.

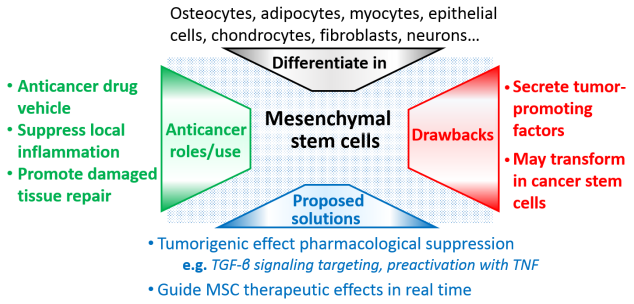

Figure 1. *Graphical abstract of the review*

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