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Can mesenchymal stem cells be used as a future weapon against breast cancer?

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KEYWORDS

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Conditionally replicating adenoviruses (CRAds)

Abstract *Background:* Mesenchymal stem cells (MSCs) are recruited to the stroma of cancers. They interact with cancer cells to promote invasion and metastasis or to suppress tumor growth. The unique tumor-homing capacity of MSCs makes them a promising vehicle to deliver various anticancer agents.
Aim: The aim of this study was to detect the possibility of using mesenchymal stem cells as a future weapon against breast cancer.
Methods: PubMed, PubMed central, Springer and Cochrane databases were searched using specified terms.
Results: Literature search yielded 17 manuscripts: seven of which suggested the use of MSCs in breast cancer therapy, while six studies raised the possibility that MSCs may promote tumor growth and four other studies assumed a dual role for MSCs.
Conclusions: The role of MSCs in breast cancer therapy is still debatable. We recommend future research in the field of MSCs in Alexandria University as it is our hope in the fight against breast cancer.

Contents

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1. Introduction

Breast cancer is the most common malignancy among females throughout the world. Combined therapeutic modalities including surgery, chemotherapy, radiotherapy, endocrine and targeted therapies are the mainstay of treatment. However, they may lead to unsatisfactory outcomes, mainly due to the difficulty in accessing tumor sites, the dispersed nature of the disease and the toxicity of the treatment.[1]

MSCs were originally isolated from bone marrow, and later from adipose tissues and many other organs. These cells are capable of self-renewal and differentiation into bone, fat, or cartilage cells under appropriate conditions.[2]

MSCs are often involved in tissue remodeling after injury or chronic inflammation. Tumors resemble chronic wounds or "wounds that never heal".[2] The recruited MSCs and their derivative cancer-associated fibroblasts interact with cancer cells to promote invasion and metastasis. On the other hand, the unique tumor-homing capacity of MSCs renders them a promising vehicle for adequate and specific delivery of various anticancer agents.[2]

This article discusses the potential of using MSCs as a weapon against breast cancer.

2. Methods

PubMed, PubMed central, Springer and Cochrane databases were searched using specified terms. Key words used were mesenchymal stem cells, mesenchymal stem cells and breast cancer, breast cancer.

Inclusion criteria Publications on mesenchymal stem cells were included in the study. Reference lists of reviews and research articles were examined for relevant publications.

Exclusion criteria Case reports, letters, reviews without original data, non-English language papers, abstracts, and articles with incomplete data were excluded.

3. Results and discussion

Various studies have reported contradicting results as regards the role of MSCs in breast cancer. While several studies support the growth promoting effects of MSCs, others suggest that they act as tumor suppressive agents. A dose dependent effect has been proposed to explain these varying roles; at lower cell numbers (relative to the number of tumor cells) human MSCs are more likely to inhibit tumor growth, whereas at higher cell numbers they promote tumor growth.[3] Alternative theories state that these varying roles might be related to the presence of different subpopulations among MSCs, individual variations in the physiological immune status of the donors, and differences in MSC isolation and culture methods.[4] Other mechanisms have been reported as well including chemokine signaling, modulation of apoptosis, vascular support, and immune modulation.[5]

3.1. Suppression of tumor growth

The role of MSCs as tumor suppressors depends mainly on their involvement in tissue remodeling after injury or chronic inflammation. MSCs are recruited specifically to the tumor site to form tumor stroma.[2]

The avid tropism of MSCs to tumors, as well as their ability to engraft, survive, and proliferate in the tumor architecture, renders them prime cellular vehicles for the delivery of antineoplastic therapy to both primary tumors and their metastases.[4]

Brennen et al.[1] demonstrated that MSCs engrafted in tumors could act as stromal precursor cells and successfully function as cellular vehicles for gene delivery and contribute to the local production of biological agents.[1]

A number of approaches have been utilized in this regard. For example the use of genetically modified MSCs to kill malignant cells has shown positive results.[6] (Fig. 1)[4] Systemically-infused interferon beta (IFN-β) expressing bone marrow-derived MSCs successfully reduced the growth of human breast cancer cells from MDA-MB-231 line upon engraftment into the tumor stroma.[6]

BALB/c murine MSCs home specifically to mouse 4T1 sites and deliver murine IFN-β to the tumors sufficient to inhibit breast cancer growth through inactivation of the Stat3 signaling pathway. In addition, MSC/IFN-β/GFP treatment also showed signs of an improvement in cell-mediated immunity as indicated by the increased numbers of splenic mature dendritic cells and decreased numbers of regulatory T lymphocytes.[7]

Liu et al. studied the effects of hUMSCs/IL-18 (human umbilical cord MSCs genetically modified with interleukin-18 gene) on the growth, migration and invasion of two breast cancer cell lines *in vitro*. The results showed that hUMSCs/IL-18, but not hUMSCs, significantly inhibited the growth, migration and invasion of human breast cancer cell lines MCF-7 and HCC1937 *in vitro*. Flow cytometric analysis showed that hUMSCs/IL-18 significantly increased the percentage of cells in the G0/G1 phase but decreased that in the S and G2/M phase.[1]

The second approach was the use of MSCs as intermediate carriers for conditionally replicating adenovirus (CRADs) to target metastatic breast cancer *in vivo*.[8] Stoff-Khalili et al. concluded that hMSCs may be an effective platform for targeted delivery of CRAds to distant cancer sites such as metastatic breast.

They investigated the *in vivo* anti-tumor activity of hMSC-Ad5/3.CXCR4 (C-X-C chemokine receptor 4). Mice injected with hMSC-Ad5/3.CXCR4 had significantly lower mean lung weights than Ad5/3.CXCR4 treated or control untreated mice. Thus, the tumor burden of breast cancer metastases in the lungs was significantly less in animals treated with CRAd loaded hMSCs than with the CRAd alone. Furthermore, treatment with hMSC-Ad5/3.CXCR4 improved survival of mice bearing breast cancer metastases in the lungs.[8]

MSCs were found to inhibit tumor growth through a variety of other mechanisms including secretion of paracrine factors. Ma et al.[4] studied the effect of hUMSCs on cancer stem cells *in vitro*. The results showed that hUCMSCs inhibited the growth of breast cancer cell lines (MDA-MB-231 and MCF-7), and primary breast cancer stem cells (CSCs) in a dose-dependent manner. The underlying mechanism is likely related to cell cycle arrest and induction of tumor cell apoptosis.[4] HUMSCs were also found to inhibit the development of pulmonary metastases from breast adenocarcinoma MDA-MB-231 cell line *in vivo* in mice. Long-term *in vivo* bioluminescence imaging of intravenously injected MSCs genetically labeled with luc2 gene showed distribution of MSCs to the

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