AMERICAN JOURNAL OF MEDICAL AND CLINICAL SCIENCES, 2023
VOL 8, NO. 3, PAGE 1 – 6

RESEARCH ARTICLE

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Mesenchymal Stem Cell-Based Therapy: Targeting Triple-Negative Breast Cancer

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ABSTRACT

Across the globe, breast cancer (BC) is the most frequently identified cancer in women, with approximately 1.7 million new cases diagnosed annually. Despite current advances in cancer treatment and detection technology, breast cancer stem cells (bCSCs) within the tumor microenvironment have contributed to the rise in chemotherapy drug resistance and tumor relapse. As a result, BC remains a considerable public health threat and is of utmost importance to biomedical research. The emergence of cell-based therapies has provided promising potential in terms of clinical application, especially regarding tumor heterogeneity. Mesenchymal stem cell (MSC)-based therapy has been an attractive area of research due to the self-renewal and differentiation capabilities of MSCs. On the other hand, the use of MSCs in cancer treatment and human clinical trials is restricted by contradictory results in preclinical investigations. This review summarizes the unique attributes of MSCs and their mechanistic potential in targeting triple-negative breast cancer (TNBC). It addresses preclinical risk factors associated with MSC-based therapy and future direction to improve therapeutic utility.

ARTICLE HISTORY

Received 19 April 2023
Accepted 24 May 2023
Published 30 May 2023

KEYWORDS

Adult stem cells; Breast cancer; Breast cancer stem cells; Cancer stem cells; Mesenchymal stem cells; Metastatic breast cancer; Triple-negative breast cancer; Tumor microenvironment.

Abbreviations

BC: Breast Cancer; bCSCs: Breast Cancer Stem Cells; BCRAT-Breast Cancer Risk Assessment Tool; CAFs: Cancer Associated Fibroblasts; CSCs: Cancer Stem Cells; DCIS: Ductal In Situ Carcinoma; ECM: Extracellular Matrix Components; EGFR: Epidermal Growth Factor Receptor; ER: Estrogen; EV: Extracellular Vesicles; FGF: Fibroblast Growth Factor; IL-10: Interleukin-10; MBC: Metastatic Breast Cancer; MRI: Magnetic Resonance Imaging; MSCs: Mesenchymal stem cells; NCI: National Cancer Institute; PR: Progesterone; TGF-β: Transforming Growth Factor Beta; TME: Tumor Microenvironment; TNBC: Triple Negative Breast Cancer; TRAIL: Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand; VEGF: Vascular Endothelial Growth Factor.

Introduction

In terms of screening, the most well-known prediction tool is the Breast Cancer Risk Assessment Tool (BCRAT), also known as the Gail model. Developed at the National Cancer Institute (NCI), this tool considers age, age of first menstruation, family history, along with a couple of other factors to project both the 5-year and lifetime risk of developing BC in women [8,9]. The Gail model is said to have the most accurate risk prediction in women without a strong familial predisposition [10]. Nevertheless, mammography is predominantly utilized for screening and early detection of BC, although magnetic resonance imaging (MRI) and ultrasonography have also been implemented throughout the last decade [5,11]. While mammography is currently the only recommended screening technique with evidence of decreased BC mortality, women with dense breast tissue are often subject to less accurate detection; thus, BC screening via MRI and ultrasonography shows promise for women with dense breast tissue [5,11].

Moreover, ductal, and lobular hyperproliferation inside the breast typically functions as the initiation step in the formation of benign tumors or malignant carcinomas [5]. Carcinomas formed within the breast ducts or lobules are generally referred to as adenocarcinomas, which are labeled as either "in situ" or "invasive," depending on whether they have spread [12]. Ductal carcinoma in situ (DCIS), for instance, is a form of pre-cancer that is localized to the milk duct. However, invasive (or infiltrating) BC has migrated into the surrounding breast tissue [12].

The Tumor Microenvironment

The tumor microenvironment (TME) also promotes the development and progression of BC. These microenvironments are comprised of the tumor stroma, blood vessels, inflammatory/immune cells, tissue cells, as well as extracellular matrix (ECM) components [13-15]. Cancer-associated fibroblasts (CAFs) within the TME serve as a source of growth factors (including transforming growth factor beta (TGF-β) and fibroblast growth factor (FGF) and signaling molecules that aid in the proliferation of cancer cells [15,16]. In addition, the TME can suppress the immune system's ability to detect and rid the body of cancerous cells. This mechanism arises from the production of immune-suppressive factors, such as chemokines and cytokines, which prevent proper immune response and evasion [15,16]. Furthermore, the TME can manufacture products that encourage angiogenesis (providing additional nutrients and

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oxygen for cancer cell proliferation) [13-16]. ECM components within the TME also play a major role in BC progression through the promotion of cancer cell motility. For example, the dynamic structure of the ECM comprises a three-dimensional scaffold of proteins, glycoproteins, polysaccharides, and proteoglycans. Using invadopodia or pseudopodia, cancerous cells are able to migrate and invade tissue by interacting with the ECM scaffold in an integrin-mediated fashion [17]. Proteolytic remodeling of ECM components within the TME can also aid in cancer cell motility by altering stiffness gradients within the ECM, causing cancerous cells to migrate toward areas of increased stiffness, which promotes tissue invasion and the progression of metastatic disease [18].

Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) is not inherently limited to a localized tumor site (can metastasize) and accounts for an estimated 10-15% of all BC cases [19]. This type of BC is named for the fact that the cancer cells do not contain estrogen (ER) or progesterone (PR) receptors while also producing a decreased amount of the HER2 protein compared to other forms of BC; thus, the cancer cells receive three "negative" test results [19,20]. In terms of susceptibility, TNBC tends to afflict women younger than the age of forty, Black women, and those with a mutation in the BRCA1 gene [20]. Compared to other BR subtypes, TNBC is generally more aggressive [21].

Current Treatment Options

There are several treatment options for BC, yet treatment is typically dependent upon the stage (severity) and type of BC [22]. Surgery to remove localized tumors and surrounding tissue is the most common form of treatment in non-MBC. Chemotherapy, by contrast, is a form of drug treatment that is often used prior to surgery as an attempt to shrink existing tumors. However, both chemotherapy and radiation treatment are routinely used after surgery to kill any remaining cancerous cells [22]. TNBC is limited in terms of treatment options due to its hormone receptor status. Since TNBC lacks ER and PR receptors and produces negligible amounts of the HER2 protein, this form of BC cannot be treated with hormone therapy or anti-HER2 drugs [23]. In most instances, and depending upon the stage of TNBC, surgery to remove small tumors along with adjuvant chemotherapy is a common method of treatment. The latter and more advanced stages of TNBC often undergo chemotherapy followed by targeted drugs, immunotherapy, or antibody-drug conjugate [24].

The Potential of Stem Cell-Based Therapy

The ability of self-renewal and differentiation are two notable characteristics of stem cells [25]. That said, there are two primary stem cell types: embryonic stem cells and adult stem cells. Embryonic stem cells are acquired from the inner cell mass of the blastocyst, have the potential to generate any fully differentiated cell of the body, and can even develop into a complete embryo. This feature brings about both legal and ethical considerations regarding the use of human embryonic stem cells [25,26]. Conversely, the use of adult stem cells is less controversial. Adult mesenchymal stem cells (MSCs) are known for their multipotency and can be utilized in a wide variety of clinical applications, including BC treatment [25]. Nonetheless, TNBC tends to proliferate and spread at faster rates compared to other forms of invasive BC [20,21]. With fewer treatment options and a rather unfavorable prognosis, the use of adult MSCs demonstrates promising potential in the fight against TNBC [27].

Cancer Stem Cells

Over the past several decades, diagnostic biomarkers have been utilized to identify different cell types that are susceptible to disease progression and post-therapeutic relapse in cancer patients [28]. Cancer stem cells (CSCs), for instance, are a subset of tumor cells that can arise from either differentiated cells or adult tissue-resident stem cells. That said, the use of radiation and chemotherapy can alter the tumor microenvironment (TME), leading to increased plasticity in CSCs [28]. This characteristic can alter both the phenotypic and functional aspects of CSCs, while also promoting stemness. Stemness is important in the maintenance of homeostasis between proliferation, quiescence, and generation of differentiated cells, which ultimately sustains the progression of cancer [28,29].

The Origin of Breast Cancer Stem Cells

There are two closely linked hypotheses that attempt to delineate the origin of breast cancer stem cells (bCSCs) and their role in tumor heterogeneity [30]. The stochastic model, also referred to as the clonal evolution model, suggests that random genetic events and mutation in breast epithelial cell types drive the neoplastic process and evasion of apoptosis [31]. Coevolution with the TME and further genetic and epigenetic changes within neoplastic cells also influences tumor heterogeneity [32].

On the other hand, the cancer stem cell hypothesis postulates that CSCs are responsible for the initiation and cell proliferation of neoplasms. This hypothesis also proposes that CSCs are capable of self-renewal and differentiation into various cell types within the tumor [33]. Stem cells within normal adult breast tissue, while relatively dormant in nature, can form progenitors that can transform into functional cells of the breast. More specifically, progenitors can differentiate into estrogen receptor-positive and estrogen receptor-negative epithelial breast cells [31]. In essence, the cancer stem cell hypothesis supports the idea that tumorigenesis relies on the dysregulation of self-renewal in tissue stem cells (or their progenitors); correspondingly, the development of breast cancer (BC) is highly influenced by stem cell-like properties of cellular components (e.g., self-renewal capability) [31,34].

Attributes of Mesenchymal Stem Cells

Adult mesenchymal stem cells (MSCs) are stromal cells that have the ability of self-renewal and differentiation along distinct mesenchymal lineages in vitro (e.g., osteocytic, chondrocytic, and adipogenic) [35]. These non-hematopoietic cells were initially derived from bone marrow, in which they were granted a degree of high plasticity. Most clinical studies to date have utilized bone marrow derived MSCs, yet harvesting cells from bone marrow is a rather invasive and limited procedure [35,36]. However, MSCs can also be isolated from a variety of other sources, including adipose tissue, endometrial polyps, fallopian tubes, umbilical cord blood, cruciate ligament, and even menstrual blood [26,37].

In recent years, adipose tissue, and umbilical cord blood have drawn significant attention as alternative sources of MSCs [38]. Compared to harvesting from bone marrow, MSCs derived from adipose tissue produce higher initial cell yields and more favorable proliferation in vitro. In addition to the ease of tissue collection, MSCs obtained from adipose tissue also demonstrate similar differentiation ability and immunophenotype as opposed to those isolated from bone marrow [38,39]. Moreover, umbilical cord blood is another accessible and plentiful source of MSCs, as the cells can be isolated [non-invasively] immediately following placenta extraction [39]. Umbilical cord blood-derived MSCs found within the adherent layer of cell culture exhibit fibroblast-like morphology, which produces the same mesenchymal progenitor cell-related antigens (e.g., CD13, CD29, SH3, SH4, CD90, and ASMA) as MSCs harvested from bone marrow [40]. On the contrary, it is crucial to note that MSCs derived from various tissue types exhibit different cell surface markers, which directly contribute to their differentiation potential [38]. That said, MSCs can undergo differentiation pathways that result in either mesodermal, endodermal, or ectodermal lineages. These pathways are regulated by in vitro conditions and genetic events associated with various transcription factors [25,42].

MSCs in Regenerative Medicine

Considering their ability to travel to damaged tissue, modify host immune response, and differentiate into numerous cell types, MSCs demonstrate promising potential in the realm of regenerative medicine [43]. For instance, MSCs have the capability of regulating lymphocytes through the exertion of immunomodulatory and anti-inflammatory properties [44,45]. More specifically, current research addresses the role of MSCs in the regulation of T-cell proliferation and function, helper T-cell activity, B-cell suppression, as well as natural killer cell inhibition [44-47]. In addition to tissue repair and immunomodulation, MSCs can also induce paracrine effects through a variety of growth factors, cytokines, and chemokines, which function to repair tissue and generate new blood vessels (promoting nutrient exchange) [48]. MSCs also demonstrate promising potential to treat cancer through gene therapy, as these cells can be genetically engineered to express therapeutic RNA or proteins [49].

Mechanistic Aspects of MSCs

MSCs have attained compelling attention regarding cancer therapy due to their unique characteristics and regenerative potential [43]. More specifically, MSCs can play a role in paracrine signaling, immune modulation, tumor homing and localization, differentiation, and even drug delivery. Nevertheless, the molecular mechanisms utilized by MSCs to exert impact on cancer cells are still under study.

Paracrine signaling is utilized by MSCs to interact within adjacent cells, including cancerous cells. Through the secretion of soluble factors, such as chemokines, cytokines, extracellular vesicles, and numerous growth factors, MSCs can activate various receptor-mediated signaling pathways in neighboring cells [50]. For example, MSCs have the potential to secrete anti-inflammatory factors, including transforming growth factor beta (TGF-β) and interleukin-10 (IL-10), which function to mediate immune response (e.g., suppression and polarization of immune cells) toward an anti-inflammatory phenotype. This modulation can generate an environment more capable of tissue repair [15,16,50]. MSCs can also secrete factors that regulate angiogenesis, such as vascular endothelial growth factor (VEGF) and angiostatin. These factors can contribute to tissue regeneration and can even limit tumorigenesis by inhibiting the formation of new blood vessels [13-16]. Furthermore, paracrine signaling via MSCs can secrete factors that inhibit the activation and proliferation of T-cells and even factors which promote programmed cell death, such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [46, 51]. TRAIL can initiate apoptosis in cancer cells, while producing little effect on normal cells [51]. The tumor microenvironment (TME) and source of MSCs can affect the profile of secretion factors produced [15,16].

Specific receptors and extracellular vesicles (EV) within the TME enable MSCs to travel toward tumor sites, where they may confine amongst the tumor stroma and exert therapeutic effects (either directly to cancerous cells or indirectly through modulation of the TME) [51]. That said, chemokines and growth factors within the tumor stroma function as chemoattractants for MSCs, which guide them to the tumor site. MSCs can exhibit specific adhesion molecules and receptors that facilitate these interactions within the TME [51]. In addition, MSCs can undergo genetic engineering to express specific surface receptors or ligands that can recognize tumor cells or components within the TME. This modification enables MSCs to act as targeted delivery systems and bolsters their ability to home to the tumor site [49].

Targeting Triple-Negative Breast Cancer

MSCs have the potential to target triple-negative breast cancer (TNBC) through several strategies. For one, genetic modification of MSCs can be utilized to specifically recognize and bind to TNBC cells [49]. More specifically, the epidermal growth factor receptor (EGFR) is generally overexpressed on TNBC cells; thus, genetically engineering MSCs to target EGFR could allow for the delivery of therapeutic cargo to or immune response modulation against the TNBC tumor(s) [49,52]. This inherent tumor-homing capability also enables drug-loaded MSCs to transport anti-cancer medicines or therapeutic agents to the TNBC tumor sites [52]. Moreover, MSCs can influence the TME in TNBC tumor sites by regulating inflammation and immune response, as well as simulating angiogenesis [13-16]. MSCs can also be used in combination with other cancer treatment options, such as surgery, chemotherapy, and radiation, which may have the potential to improve drug delivery and enhance the anti-tumor response [52].

However, it is crucial to consider the challenges and limitations when utilizing MSCs to target TNBC. For instance, TNBC is particularly heterogeneous, with several diverse subtypes and genetic alterations. That said, the use of MSC-based therapies may be limited depending on the specific aspects of the TNBC subtype being targeted [53]. Additionally, MSCs can migrate and localize in healthy tissue. This potential and rather unintended interaction may result in adverse effects,

thus careful supervision of MSC distribution is necessary [52]. Another limitation of MSC-based therapy is the relatively limited engraftment and endurance of MSCs within the TME. Physical blockages, immunosuppressive effects, and the general atmosphere of the TME pose a threat to the migratory capacity of MSCs [15, 16]. Regulatory requirements and securing proper approvals for clinical trials are also critical components to consider that can be both time-consuming and resource intensive.

Future Direction

Mesenchymal stem cells (MSCs) have exhibited vast therapeutic and diagnostic potential in terms of breast cancer (BC) research. MSC-based gene therapy to specifically target tumor cells and the application of biomarker development make MSCs a promising tool for BC diagnosis, prognosis, and treatment [49,54]. However, the therapeutic and diagnostic utility of MSCs is limited due to contradictory results of their tumor promotion and suppression abilities [55,56]. Therefore, further research is necessary to grasp a better understanding of the mechanisms of MSCs and their function in the tumor microenvironment (TME). More specifically, the differentiation, mobilization, immunomodulatory, and tumor-homing mechanisms of MSCs are rather complex processes that display favorable potential in clinical applications and regenerative medicine [25]. In sum, it is important to consider that the limitations in using MSCs to target triple-negative breast cancer (TNBC) are not insurmountable, and ongoing research and preclinical studies are essential to the safety and efficacy of MSC-based therapy.

Summary

This review addresses the therapeutic potential of mesenchymal stem cells (MSCs), with an emphasis on their role in the diagnosis and treatment of triple-negative breast cancer (TNBC). Current evidence suggests that breast cancer stem cells (bCSCs) are a major contributor to drug resistance and tumor relapse within cancer patients [30]. To develop both functional and successful treatment alternatives, it is of vital importance to understand the complex interplay between bCSCs and the tumor microenvironment (TME). The TME plays a crucial role in the self-renewal, differentiation, and proliferation of bCSCs, through the utilization of extracellular vehicles and extracellular matrix (ECM) components, as well as through the growth factors produced by immune cells and cancer-associated fibroblasts (CAFs) [16,57]. Regarding tumor heterogeneity, it is also essential to explore both bCSCs-targeted and TME-targeted treatments. That said, mesenchymal stem cells (MSCs) have several attributes which make them desirable candidates for breast cancer (BC) treatment, including their self-renewal ability, multi-differentiation capacity, and potential for genetic engineering [38,49]. On the contrary, these characteristics also make MSCs capable of promoting tumor growth and metastasis [56]. The ability to proceed with human clinical trials is limited. Therefore, the need for future research on the relationship between MSCs and bCSCs is critical in the development of more effective treatment methods, with the hope of improving patient prognosis in those suffering from TNBC.

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