Journal of Stem Cell Research

Genesis-JSCR-6(2)-73
Volume 6 | Issue 2
Open Access
ISSN: 2582-8797

Usage of Stem Cells for Treatment of Triple Negative Breast Cancer

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Citation: Wright J and Gallicchio VS, Usage of Stem Cells for Treatment of Triple Negative Breast Cancer. J Stem Cell Res. 6(1):1-9.

Received: June 25, 2025 | **Published**: July 10, 2025

Abstract

The purpose of this research is to further investigate the usage of stem cells in treating triple negative breast cancer. Triple negative breast cancer is a type of cancer most found in women; however, the cancer is emphasized by its aggressive and poor prognosis to current available treatments. Equally important is the little-known causation for this type of breast cancer as it has yet to be determined the precise underlying factor. Increasing experiments and findings have led to the possibility of implementing stem cells in treatments with overall benefits for a woman's future health.

Keywords

Stem cells; Triple negative breast cancer; Treatments.

Abbreviations

- **TNBC** - triple negative breast cancer
- **BSCS** - breast cancer stem cells
- **CSCs** - cancer stem cells
- **DALYs** - disability-adjusted life years
- **IL** - interleukin
- **TRAIL** - TNF-related apoptosis-inducing ligand
- **SCF** - Stem Cell Factor

Research Article | Gallicchio VS, et al. J Stem Cell Res.2025, 6(2)-73.
DOI: https://doi.org/10.52793/JSCR.2025.6(2)-73

- **CCL5** - Chemokine ligand 5
- **CT** - chemotherapy
- **TEM8** - tumor endothelial marker 8

Introduction

Triple negative breast cancer is a rare, less widely known type of breast cancer, although it crucially targets many women while lacking a straightforward, effective treatment plan. Patients diagnosed with TNBC, compared to those diagnosed with other breast cancer subtypes, have relatively poor outcomes due to high tumor aggressiveness and lack of targeted treatment [1]. Triple negative breast cancer patients have less targeted treatments due to the aggressiveness of this specific cancer, therefore these patients see less than ideal outcomes. Triple-negative breast cancer (TNBC), a specific subtype of breast cancer that does not express estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER-2), has clinical features that include high invasiveness, high metastatic potential, proneness to relapse, and poor prognosis [2]. The outcry and need for an effective treatment plan for triple negative breast cancer has become an urgent matter. Breast cancer is the most frequent malignancy in women worldwide, and triple-negative breast cancer (TNBC) patients have the worst prognosis and highest risk of recurrence. The therapeutic strategies for TNBC are limited. It is urgent to develop new methods to enhance the efficacy of TNBC treatment [3]. From a medical standpoint triple negative breast cancer is an area of unmet, lacking medical necessity (Figure 1).

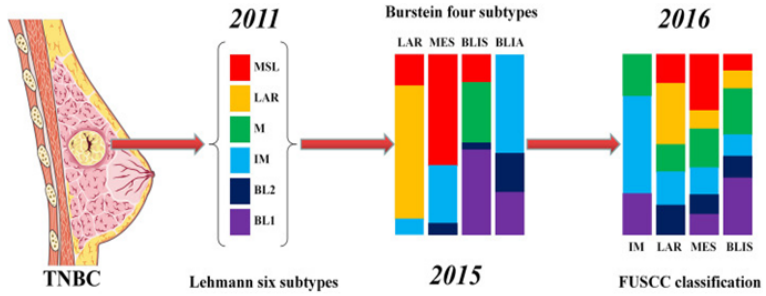

Figure 1: The subtypes and classifications associated with triple negative breast cancer found by Lehman [2].

The biggest issue with triple negative breast cancer is that it lacks ER, PR, and HER2 expression. This in turn makes it significantly harder to treat the specific type of hormone related to the cancerous cells, additionally triple negative breast cancer not sensitive to HER2 endocrine therapy. Typical triple negative breast cancer regimes still lack in their convenience, effective killing of cancerous cells, and overall future effects. Traditional regimes are costly and time consuming without providing a definite cure of the cancer after treatment. Furthermore, traditional TNBC regimes destroy the entire body's immune system at the conclusion of treatments along with other issues for the human body such as hair loss and neuropathy.

Discussion

Although many types of cancer that affect many different areas in the human body plague humans throughout the world, breast cancer has become one of the most common types in women. On a more notable level, the subtype of triple negative breast cancer is on the rise without a clear, concise treatment

DOI: https://doi.org/10.52793/JSCR.2025.6(2)-73

plan including definite resolutions to ultimately killing the tumors without future relapse. There were approximately 6,85,000 deaths worldwide and 2.3 million new breast cancer cases in women in 2020. Breast cancer is the most common cancer globally, affecting 7.8 million people at the end of 2020. Compared to other cancer types, breast cancer causes more women to lose disability-adjusted life years (DALYs). Worldwide, women can develop breast cancer at any age after puberty, but rates increase with age. The maintenance of mammary stem cell stemness is disrupted in TNBC, governed by signaling cascades controlling healthy mammary gland growth and development [4].

The statistics of breast cancer are alarming which further emphasizes the need of a treatment pathway that can immediately target and destroy the cancerous cells causing the development of this cancer. On a smaller scope, triple negative breast cancer statistics are scary, sheerly due to the low survival rates or full recovery of women diagnosed with this subtype of breast cancer. Triple-negative breast cancer (TNBC) is the most complex, aggressive, and fatal subtype of breast cancer. Owing to the lack of targeted therapy and heterogeneous nature of TNBC, chemotherapy remains the sole treatment option for TNBC, with taxanes and anthracyclines representing the general chemotherapeutic regimen in TNBC therapy. But unfortunately, patients develop resistance to the existing chemotherapeutic regimen, resulting in approximately 90% treatment failure [5]. Due to the high resistance to chemotherapy identified in triple negative breast cancer patients amplifies the need for an effective treatment plan.

Treatment of triple-negative breast cancer (TNBC) remains challenging due to the underlying heterogeneity of this disease coupled with the lack of predictive biomarkers and effective targeted therapies.

Intertumoral heterogeneity, particularly enrichment for breast cancer stem cell-like subpopulations, has emerged as a leading hypothesis for systemic therapy resistance and clinically aggressive course of poor prognosis TNBC. A growing body of literature supports the role of the stem cell renewal Hedgehog (Hh) pathway in breast cancer [6]. Less widely known is the new research of stem cell usage to treat triple negative breast cancer. Triple-negative breast cancer (TNBC) is the most heterogeneous breast cancer subtype. Partly due to its heterogeneity, it is currently challenging to stratify TNBC patients and predict treatment outcomes. We identified five cytokines that correlate with good clinical outcomes: interleukin (IL)-1α, TNF-related apoptosis-inducing ligand (TRAIL), Stem Cell Factor (SCF), Chemokine ligand 5 (CCL5 also known as RANTES), and IL-16 [7]. In addition, to the urgent need for another, new triple negative breast cancer treatment is the fact that with the current treatments, they are unpredictable for women's future health. With stem cells being one of the cytokines correlating to good clinical health prior to the conclusion of all treatments, this promises a potential lead on using stem cells to treat triple negative breast cancer to maintain that good cytokine.

By utilizing stem cells during the remission time of a cancer treatment, current research has found it to help women to recover quicker or have less of the horrible side effects following current breast cancer treatment regimes. Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks receptors for targeted therapy. Consequently, chemotherapy is currently the mainstay of systemic treatment options. However, the enrichment of cancer stem cells (CSC, a subpopulation with stem-cell

characteristics and tumor-initiating propensity) promotes chemo-resistance and tumorigenesis, resulting in cancer recurrence and relapse. Furthermore, toxic side effects of chemotherapeutics reduce patient wellbeing [9]. One such idea of incorporating stem cell use would be to take stored stem cells from children of triple negative breast cancer patients, specifically moms. Some parents at the time of their child's birth opt to pay for a subscription type service where the stem cells located in their baby's umbilical cord blood is stored in blood banks, in case of future health issues where the child may need transfusions.

Stem cells are currently under investigation for their effective long-term treatment plan for triple negative breast cancer patients. Triple-negative breast cancer (TNBC) is an aggressive disease with a short median time from relapse to death. The increased aggressiveness, drug resistance, disease relapse, and metastasis are associated with the presence of stem cells within tumors. Several stem cell markers, such as CD24, CD44, CD133, ALDH1, and ABCG2, have been reported, but their roles in breast cancer tumorigenesis remain unclear. Binding assays revealed the specific uptake of the nanoparticles to breast cancer stem cells (BCSCs) and TNBC cells. Functional assays showed that cancer cell migration was reduced, miR21 expression was inhibited, and downstream tumor suppressor PTEN and PDCD4 expressions were upregulated [10]. Although, still not fully clear as this method is still being tested, binding assays of nanoparticles are an effective uptake for breast cancer stem cells and more specifically for triple negative breast cancer cells. Additionally, cancer cell migration throughout the body was reduced and tumor expression was halted with the usage of nanoparticles.

The use of single-cell mass cytometry has become a newly found discovery. Additionally, an RGD-included nanoparticle (CS-V) promotes doxorubicin efficacy against MDA-MB-231 spheroid cells which have been highlighted for their concern in breast cancer-related death in women. By using single-cell mass cytometry, it was observed that stemness in spheroid-forming cells derived from MDA-MB-231 cells was significantly increased after doxorubicin administration and up-regulated integrin αvβ3 expression was also observed. An RGD-included nanoparticle (CS-V) was designed, and it was found that it could promote doxorubicin's efficacy against MDA-MB-231 spheroid cells. The above observations suggested that the combination of RGD-included nanoparticles (CS-V) with the chemo-drug doxorubicin could be developed as a potential therapy for breast cancer [11]. The use of stem cells to treat triple negative breast cancer has previously been known to be extremely difficult to use, but through amino acid metabolism it has become more of a possible task. Cancer stem cells (CSCs) are the most intractable subpopulation of triple-negative breast cancer (TNBC) cells…These findings indicate that clinically relevant eradication of CSCs could be achieved with a strategy that targets CSC-specific vulnerabilities in amino acid metabolism [11].

Many treatments are currently being tested for the efficiency and effectiveness in treating triple negative breast cancer. Among these tested treatments is the newfound use of stem cells. Taxane and anthracycline-containing chemotherapy (CT) is currently the main systemic treatment option for TNBC, while platinum-based chemotherapy showed promising results in the neoadjuvant and metastatic settings. An early arising of intrinsic or acquired CT resistance is common and represents the main hurdle for successful TNBC treatment. Numerous mechanisms were uncovered that can lead to the development of chemoresistance. These include cancer stem cells (CSCs) induction after neoadjuvant chemotherapy (NACT), ATP-binding cassette (ABC) transporters, hypoxia and avoidance of apoptosis, single factors such

as tyrosine kinase receptors (EGFR, IGFR1), a disintegrin and metalloproteinase 10 (ADAM10), and a few pathological molecular pathways. Emerging therapies allow to select specific antibiotics that alone or by integrating the conventional therapeutic approach may overcome/hinder chemoresistance [12]. Using adipose-derived stem cells shows the future possibility for using stem cells to fight against cancerous cells in triple negative breast cancer patients. Adipose-derived stem cell exosomes represent a potential tool in targeting triple-negative breast cancer cells at three main levels: the tumor core, the tumor microenvironment, and surrounding tissues, including metastasis [13].

Triple-negative breast cancer (TNBC), the deadliest form of this disease, lacks a targeted therapy. TNBC tumors that fail to respond to chemotherapy are characterized by a repressed IFN/signal transducer and activator of transcription (IFN/STAT) gene signature and are often enriched for cancer stem cells (CSCs). We have found that human mammary epithelial cells that undergo an epithelial-to-mesenchymal transition (EMT) following transformation acquire CSC properties. These mesenchymal/CSCs have a significantly repressed IFN/STAT gene expression signature and an enhanced ability to migrate and form tumor spheres. Treatment with IFN-beta (IFN-β) led to a less aggressive epithelial/non-CSC-like state, with repressed expression of mesenchymal proteins (VIMENTIN, SLUG), reduced migration and tumor sphere formation, and expression of CD24 (a surface marker for non-CSCs), concomitant with an epithelium-like morphology [14]. The repressed IFN/signal transducers are the reasons for TNBC poor response to chemotherapy. However, incorporating epithelial cells of humans may be a technique for better response with the use of stem cells (Figure 2).

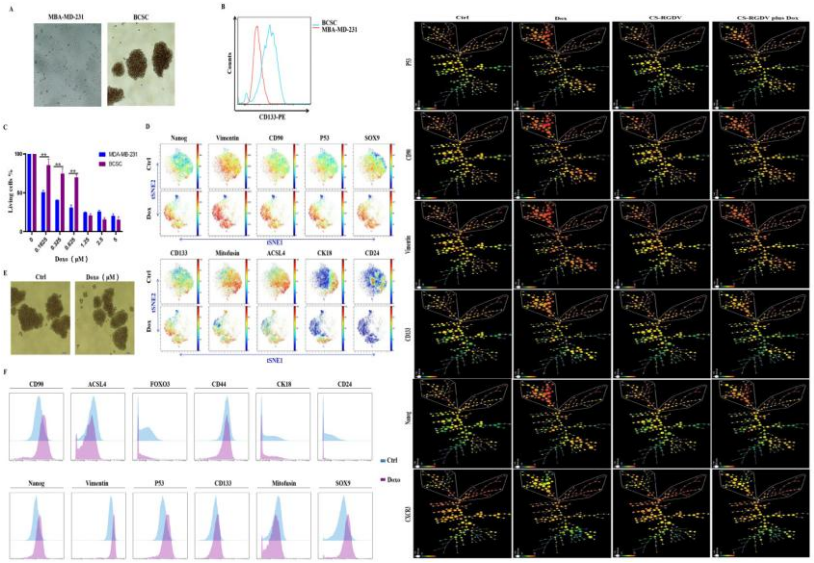

Figure 2: These images portray the single-cell mass cytometry currently under experimentation [10].

Stem cell-like treatments have been used for various diseases including breast cancer. Specifically, LINC00115 is a breast cancer stem-like cell regulator. Cancer stem-like cell is a key barrier for therapeutic resistance and metastasis in various cancers, including breast cancer, yet the underlying mechanisms are still elusive. Through a genome-wide lncRNA expression profiling, we identified that LINC00115 is robustly upregulated in chemo resistant breast cancer stem-like cells (BCSCs). Our findings uncover LINC00115 as

DOI: https://doi.org/10.52793/JSCR.2025.6(2)-73

a critical regulator of BCSC and highlight targeting LINC00115 and SETDB1 as a potential therapeutic strategy for chemotherapeutic resistant breast cancer [15]. Although it is a new technique, stem cell use is rising rapidly in the realm of treating many types of cancer.

The aggressiveness of triple negative breast cancer has made it a more complex type of cancer to find an ideal treatment to stop proliferation at the point of discovery. ALDH1+ TNBC cells exhibit higher DOT1L and H3K79me2 than ALDH1-. DOT1L maintains MYC expression and self-renewal in ALDH1+ cells. Global profiling revealed that DOT1L governs oxidative phosphorylation, cMyc targets, DNA damage response, and WNT activation in ALDH1+ but not in ALDH1- cells. EPZ-5676 reduced tumor spheres and ALDH1+ cells in vitro and decreased tumor-initiating stem cells and metastasis in xenografts generated from ALDH1+ but not ALDH1- populations…Patients diagnosed with TNBC, compared to those diagnosed with other breast cancer subtypes, have relatively poor outcomes due to high tumor aggressiveness and lack of targeted treatment. DOT1L inhibitors to target stem cell enriched TNBC [16]. EPZ-5676 was found to reduce tumors and ALDH1+ cells, but not ALDH1-. In summary, DNMT1 expression is associated with poor breast cancer survival, and it is overexpressed in TNBC subtype. The oncogenic roles of DNMT1 in TNBCs include: (1) Repression of estrogen receptor (ER) expression; (2) Promotion of epithelial-mesenchymal transition (EMT) required for metastasis; (3) Induces cellular autophagy and (4) Promotes the growth of cancer stem cells in TNBCs. DNMT1 inhibitors exert anti-tumorigenic effects against TNBC cells. DNMT1 represents an epigenetic target for TNBC cells destruction as well as to derail their metastatic and aggressive phenotypes [17].

DNMT1 is the cause of low cancer survival in patients diagnosed with triple negative breast cancer. We find that tumor endothelial marker 8 (TEM8) is abundantly expressed in TNBC and serves as a marker for VM-forming BTICs. Mechanistically, TEM8 increases active RhoC level and induces ROCK1-mediated phosphorylation of SMAD5, in a cascade essential for promoting stemness and VM capacity of breast cancer cells. ASB10, an estrogen receptor ERα trans-activated E3 ligase, ubiquitylated TEM8 for degradation, and its deficiency in TNBC resulted in a high homeostatic level of TEM8… identify TEM8 as a functional marker for VM-forming BTICs in TNBC… [18]. The specific marker, TEM8 is the main marker expressed in triple negative patients and is found to lead to the development of cancerous cells. TNBC is highly heterogeneous in terms of their cellular lineage composition and the molecular nature within each individual case. In particular, the rare and sometimes slow cycling cancer stem cells (CSCs) can provide effective means for TNBC to resist various treatments [19]. Here stems the issues in interrupting molecular signaling against unusual cell populations which lead to disease.

Contrastingly, diet has been scientifically identified to have a role in TNBC. Research has pointed to following a plant-based, whole foods diet. Simultaneously maintaining a low glycemic level has proven to contribute to longer survival rates in women previously having recovered from triple negative breast cancer. We show that a fasting-mimicking diet (FMD) activates starvation escape pathways in triple-negative breast cancer (TNBC) cells, which can be identified and targeted by drugs. In CSCs, FMD lowers glucose-dependent protein kinase A signaling and stemness markers to reduce cell number and increase mouse survival. Accordingly, metastatic TNBC patients with lower glycemia survive longer than those with higher baseline glycemia [20]. By controlling sugar intake to eating a manageable amount for the human

body to process and including periods of fasting allows the body systems to move their focus towards attacking cancerous cells.

Therefore, more and more physicians caring for triple negative breast cancer patients are beginning to promote a plant based, whole food diet as a precise and effective plan on the diet side of post cancer recovery. Most of the studies on TNBC were conducted in Western population and TNBC is reported to be more frequent in the African women [21]. Interestingly, triple negative breast cancer was most often in African American women populations, but more cases are being diagnosed in the Caucasian populations. This further points to diet as an overall issue from a health standpoint as it is one of a few similarities between these two populations. At this point, physicians are attempting to not treat the problem at hand, that being the cancer diagnosis, additionally give their patients long-term health advice to prevent a cancer recurrence at all costs.

On the other hand, stress has also been found to be a potential causation for triple negative breast cancer. Metabolic stress resulting from nutrient deficiency is one of the hallmarks of a growing tumor. Here, we tested the hypothesis that metabolic stress induces breast cancer stem-like cell (BCSC) phenotype in triple-negative breast cancer (TNBC). Glucose deprivation not only increased stress markers but also enhanced GD2+ BCSC phenotype and function in TNBC cells [22]. Mounting concerns for the role stress plays in the overall health of the body has led to conclusions that at an alarming level of stress can be harmful and cancer causing. Proven that metabolic stressors contribute to triple negative breast cancer. Metabolic stressors were found to induce autophagy in TNBC cell lines. Autophagy initiation inhibitors, SAR405 and MRT68921, showed marked synergy in their anti-proliferative activity in both chemosensitive and chemoresistant TNBC cell models. Paradoxically, positive expression of autophagosome marker LC3 was shown to be associated with better overall survival of TNBC patients [23].

It is generally believed that CSCs play an important role in cancer initiation, therapy resistance, and progression of triple-negative breast cancer (TNBC), an aggressive breast cancer subtype with poor prognosis. Thus, therapies targeting these cells would be a valuable addition to standard treatments that primarily target more differentiated, rapidly dividing TNBC cells. Recent research is moving toward cellular signaling pathways as targets and biomarkers for CSCs. The WNT pathway, the nuclear factor-kappa B (NF-κB) pathway, and the cholesterol biosynthesis pathway have recently been identified to play a key role in proliferation, survival, and differentiation of CSCs, including those of breast cancer [24]. Unfortunately, chemotherapy and treatments are becoming less helpful in fully destroying triple negative cancer cells as recurrences are the rise per patient. Triple-negative breast cancer (TNBC) is a heterogeneous, aggressive phenotype of breast cancer with associated chemoresistance. The development of chemo- or radioresistance could be attributed to diverse tumor microenvironments, overexpression of membrane proteins (transporters), epigenetic changes, and alteration of the cell signaling pathways/genes associated with the development of cancer stem cells (CSCs) [25]. Moreover, the long-term detrimental effects of chemotherapy have caused many women to altogether avoid this treatment pathway and withstand the risk of utilizing natural remedies rather than chemical-based ones. For these reasons, a new approach must be embarked on to lessen the death rates that triple negative breast cancer currently causes.

Conclusion

By experimenting and developing a more straightforward, effective treatment plan targeted towards using stem cells to treat triple negative breast cancer provides hope for a future where this subtype of cancer can be treated successfully for all affected patients. Ultimately, leading to an outcome where all patients can fully recover with little to no side effects dramatically increases quality of life going forward to fulfill their lives after cancer remission is achieved. The ability to live a healthy, cancer free lifestyle lacking the doubt of recurrence has yet to be discovered in not only triple negative breast cancer patients, but also in patients diagnosed with a variety of other cancers. Stem cell usage could just be the golden gate into this new reality.

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