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Review Article

Stem Cell Therapy in Progression of Breast Cancer-An Overview

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Abstract

Cancer is the most prevalent challenging disease, among that breast cancer is the challenging malignancy with metastasis and became primary cause of mortality. Current research focus on stem cell therapy because of its ability to target and repair of damaged tissue and reverse tumorigenesis. This has emerged as a promising avenue for the treatment of breast cancer, offering potential benefits alongside significant challenges. Here we discussed the stem cell therapy leverages and its properties to intervene in cancer progression particularly in metastasis, which is resistant to conventional treatments. Stem cells can either target directly on tumor cell or by increasing the tissue repair. Here we discussed briefly the molecular mechanisms, pathways of stem cell targets in breast cancer treatment. Here we discussed the signalling pathways which were imperative in progression of breast cancer. Despite of these challenges like tumorigenicity, immune responses, and the target delivery methods remain crucial barriers to widespread clinical application. Here in this review we summarised the current progression of stem cell therapy in breast cancer.

Keywords: *Breast Cancer; Stem Cell Therapy; Tumorigenicity*

Introduction

Stem cells are different type of undistinguishable cells and can be auto generated and can be differentiate in to other types. There are many types of stem cells like embryonic, induced pluripotent, multipotent and mesenchymal [1]. One promising new method of treating breast cancer is stem cell treatment [2]. Although it is still in the early phases of development, it could completely change how this illness is treated. Stem cell therapy involves the transplantation or use of stem cells to repair, replace, or regenerate damaged tissues [3]. The history of stem cells is a fascinating journey of discovery that has evolved over centuries, with key milestones in science and medicine. Early 20th Century - Ernst Haeckel coined Ontogeny which describes, the development of living organism [4]. Even some studies on embryology discussed regarding development of various tissues with certain cells in embryo. In 20th Century - The Scientists James Till and Ernest McCulloch from Canada identified the Hematopoietic stem cells, which produces different blood cells. This was the major breakthrough evidence of Multipotent stem cells. In 1960 some scientists understood that stem cells have potential in order to regenerate the damaged

tissues and even started exploring the foundation for stem cell therapy [5,6]. Embryonic stem cells (ESC) were isolated from mouse Embryo, in 1980 s which have the capacity to differentiate in almost every type of the cell [7]. In 1998 James Thomsom at university of Wisconsin successfully isolated the human stem cell (Pluripotent) from embryo marking crowning achievement in stem cell research [8].

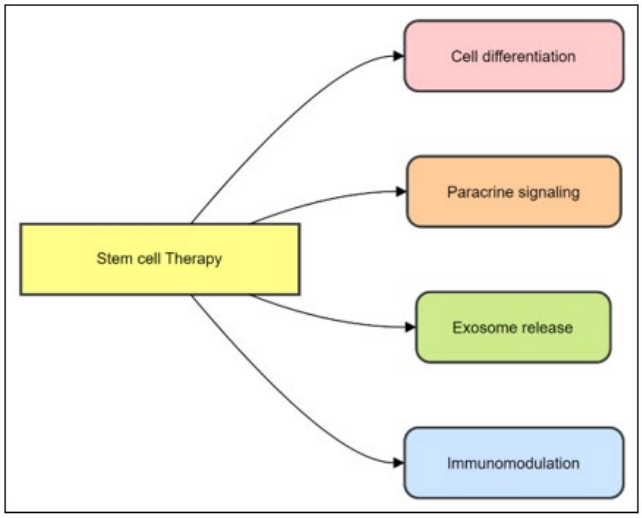

Figure 1: *An Over view of stem cell therapy.*

Role of stem cell in breast cancer

The role of stem cells is substantial in inducing breast cancer development and progression toward treatment. Cancer Stem cell exhibits special kind of ability to proliferate, differentiate into more distinct types of cells, and contribute to tumorigenesis [9,10]. Here are the implications of stem cells in breast cancer.

Tumor Initiation and Growth	Resistance to Treatment	Metastasis	Therapeutic Targeting
• Breast cancer stem cells drive Tumor Growth & Maintenance by Self - Renewing, Producing differentiated cells	• Cancer stem cells resist treatments due to DNA repair, slow cell cycles, and dormancy, leading to relapse and tumor repopulation.	• Breast cancer stem cells drive tumor initiation, metastasis, and treatment resistance by migrating, invading tissues, and forming secondary tumors.	• Research targets cancer stem cell pathways, like self-renewal and surface markers, to prevent recurrence using drugs and immune modulation.

Figure 2: *Role of stem cell.*

Since breast cancer stem cells (BSCs) have the ability to self-renew, they are essential for the development and spread of tumours. Stem cells play an important role in the early stages of development of tumor growth. Tumour cells can spread beyond the site, penetrate to other organs, and develop into secondary tumours, even BSCs also play a role in metastasis [11]. Stem cell transplants typically don't directly combat cancer. After receiving extremely high doses of chemotherapy and maybe additional treatments like radiation therapy, which are intended to destroy cancer cells, they instead help the body produce new blood cells [12]. Researchers are looking into using stem cells to better understand breast cancer and create novel treatments for the condition. According to certain research, cancer stem cells might be involved in the initiation and spread of breast cancer, and focusing on them could help treat the condition. After chemotherapy, radiation therapy, or surgery, stem cells are also being investigated as a possible means of restoring breast tissue. Nevertheless, further investigation is required to completely comprehend the potential of stem cell therapy in the management of breast cancer [13-16].

Molecular mechanisms of stem cell therapies

Wnt/β-catenin pathway

This pathway highlights the self-renewal and maintenance of stem cells (Including breast cancer stem cells (BCSCs)). This signalling pathway activation increases the proliferation and survival of stem cells, which can exaggerate tumor formation. β-catenin is an important mediator that can influence the expression of genes which are involved in metastasis and invasiveness of cancer cells [17].

Notch signalling

This signalling pathway is highly conserved as it modulates the stem cell's differentiation, proliferation, apoptosis and survival rate. Notch signalling is often dysregulated in breast cancer. Cancer stem cell (CSC) self-renewal can be encouraged by overactivation, which can lead to tumor development, metastasis, and treatment resistance. A crucial stage in metastasis, the epithelial-to-mesenchymal transition (EMT), can also be controlled by Notch. In order to eradicate CSCs and stop tumor recurrence, a therapeutic approach that targets Notch signalling in breast cancer is being investigated. However, depending on the situation, Notch can also have tumor-suppressive effects, thus precise control is essential [18].

Hedgehog (Hh) signalling

The Hedgehog (Hh) signalling system is essential for tissue homeostasis, stem cell regulation, and embryonic development. The Patched (PTCH) receptor is activated by hedgehog ligands that bind to it, such as Sonic Hedgehog [Shh], Indian Hedgehog [Ihh], and Desert Hedgehog [Dhh]. In the absence of Hh ligands, PTCH inhibits the Smoothened (SMO) protein, preventing the activation of downstream signalling [19-24].

PI3K/Akt/mTOR pathway

The PI3K/Akt/mTOR pathway is one significant signalling network that regulates several cellular processes, including as growth, survival, metabolism, and proliferation. Phosphoinositide 3kinase (PI3K) is first activated, usually by insulin or growth factor receptors like EGFR. Protein kinase B (Akt) is activated by PIP3 (phosphatidylinositol-3,4,5-trisphosphate), which is generated by PI3K. Once activated, Akt promotes cell growth and survival by phosphorylating a variety of downstream targets, including the mTOR (mechanistic target of rapamycin) pathway [25]. mTOR is a key modulator of metabolism, cell division, and protein synthesis [26]. It is present in two complexes: mTORC1 (which promotes growth and protein synthesis) and mTORC2 (which helps activate Akt and regulates cell survival). Furthermore, Ak inhibits GSK3β, a protein that negatively regulates several cellular functions. By phosphorylating numerous downstream targets, such as the mTOR (mechanistic target of rapamycin) pathway, Akt stimulates cell growth and survival once it is active [27].

Cancer stem cell theory

A subset of cancer cells with stem-like characteristics, cancer stem cells (CSCs) are essential for the development, spread, and recurrence of tumours. They can develop into distinct cell types, divide asymmetrically, and show resistance to standard treatments. CSCs have a latent condition, increased expression of ATP-binding cassette transporters, and improved DNA repair mechanisms [29]. Additionally, they can spread, trigger anti-apoptotic pathways, and lead to tumour recurrence following first therapy. Deregulated signalling pathways are essential for CSC resistance, proliferation, and maintenance. Numerous sources inside tumours or healthy tissues might give rise to cancer stem cells (CSCs) [30,31]. According to these hypotheses, which centre on cellular mutations and plasticity, CSCs may be derived from normal stem cells, dedifferentiated mature cells, cell fusion, progenitor cell transformation, tumour microenvironment (TME), and epigenetic reprogramming. Additionally, they show resistance to traditional treatments, which causes CSC-derived populations with unique characteristics to grow. Additionally, CSCs release extracellular vesicles (EVs) that increase functional diversity by influencing nearby stromal and cancer cells. These processes eventually impact tumour development by promoting growth, metastasis, immunological evasion, and therapeutic resistance [32].

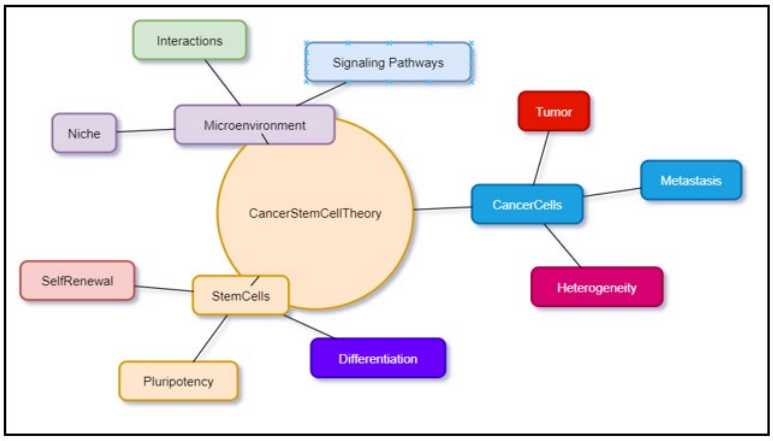

Figure 3: *Cancer stem cell theory.*

Signalling routes influencing the behaviour of CSCs

CSCs depend on certain signalling pathways to preserve their stem-like characteristics, such as survival, differentiation, and self-renewal. The dysregulation of these mechanisms mostly causes tumour development and treatment resistance [33]. Cancer stem cells (CSCs) are pivotal in tumor initiation, progression, metastasis, and recurrence.

Pathway	Role of the Pathway	Example
Wnt/β-Catenin	Encourages the preservation, growth, and self-renewal of CSCs. Aberrant activation increases tumorigenic potential.	Mutations in the APC gene cause continuous activation of the Wnt pathway in colorectal cancer, maintaining CSC populations [34].
Notch	Hyperactivation supports the survival and growth of CSCs.	Overexpression of Notch1 in breast cancer is associated with increased CSC activity and treatment resistance [35].

Hedgehog (Hh)	Fundamental to tissue homeostasis and embryonic development. Dysregulation facilitates CSC self-renewal and metastasis.	Aberrant Hh signalling is linked to the proliferation of CSCs in glioblastoma and pancreatic cancers.
PI3K/AKT/mTOR	Enhances CSC metabolism, growth, and survival. Activation increases resistance to treatment.	P13K enhances Cancer stem cell oriented carcinogenesis in lung cancer.
TGF-β	Induces epithelial-to-mesenchymal transition (EMT), increasing CSC invasiveness and adaptability.	TGF β signalling associated with colorectal cancer.

Table 1: *Signalling pathways.*

CSCs' invasive and migratory properties make them essential to metastatic cascades. They colonize unfamiliar environments, transition to a mesenchymal phenotype, and persist in circulation. Mechanisms such as quiescence, efflux pumps, enhanced DNA repair, and adaptive plasticity enable CSCs to maintain tumor heterogeneity and promote recurrence [36]. Experimental and clinical research supports the significance of CSCs in tumor development, progression, and therapy resistance. Self-renewal properties of CSCs have been confirmed by genetic labelling in glioblastoma and breast cancer, as well as transplantation of CSCs into immunocompromised mice [37]. In clinical scenarios, increased frequencies of CSC-like cells have been detected in metastatic deposits rather than primary tumor sites and were associated with poorer prognosis and increased metastatic capability in numerous neoplasias. Higher levels of CSC markers have been noted in recurrent tumors [38].

Stem cell-based therapies in breast cancer

Although research on stem cell therapy is still in its infancy, there is increasing interest in this treatment option for breast cancer. Potential uses for regeneration, targeted therapy, and comprehending the biology of the illness are only a few of the many facets of stem cells' importance in breast cancer therapy.

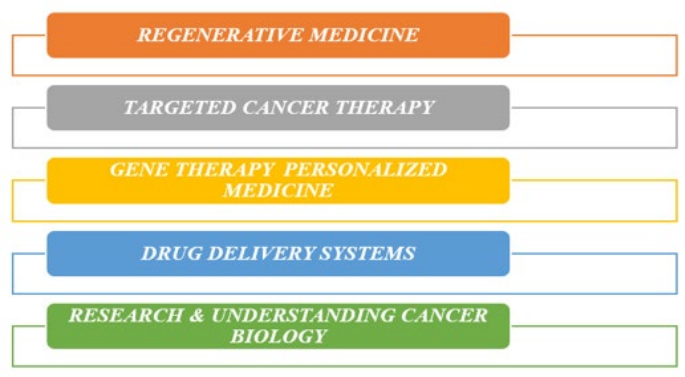

Figure 4: *Stem cell therapies in breast cancer.*

Stem cell-based treatments focus on differences and self-renewal, which provide a new approach to medical treatments. They can treat diseases such as cancer, heart disease, and neurological disorders. Additionally, stem cells modulate immune responses, encourage empathy, and reduce inflammation. The treatment of autoimmune diseases is highly improved by the use of mesenchymal and induced pluripotent stem cells.

1. **Mesenchymal stem cells (MSCs):** MSCs have the tumour-tropic properties that make them a perfect delivery vehicle in the fight against cancer. They can insert curative genes and drugs directly into the site of the cancer so that its development is reversed. The other function of MSCs is modulation of the cancer microenvironment; they produce pro-inflammatory and anti-fibrotic agents but, under specific conditions, could promote the growth of the tumor [39].
2. **Oncolytic viral therapy using stem cells (iPSCs):** Stem cells carry Oncolytic viruses, which specifically attack and eradicate cancer cells selectively. MSCs are highly effective because they are able to identify tumours. Effectiveness and potential therapeutic benefits are shown by early trials, although research to improve their efficiency is currently ongoing [40].
3. **Breast cancer stem cells (BCSCs):** Differentiation therapy reduces the chances of tumour growth whereas CSC vaccines instruct the immune system to destroy the cancer stem cells. MicroRNA methods target the pathways that are necessary for the survival and self-renewal of CSC, thus helping to inhibit metastasis and recurrence [41].
4. **Combination therapies:** Recovery rates can be improved by combining stem cell-based therapies with immunotherapy, radiation, or chemotherapy, especially when it comes to increasing tumour vulnerability to radiation and chemo.
5. **Clinical trials and advancements:** Despite challenges of comprehending their multi-faceted roles and ensuring safety, clinical trials are studying the safety and efficacy of therapies derived from stem cells in breast cancer, marking the need for rigorous controlled trials [42].
6. **Cancer stem cells: Challenges in targeting:** It is difficult to find CSCs because they lack universal markers, are heterogeneous, have phenotypic plasticity, overlap with normal stem cells, are technically limited, and lack functional validation [43]. A subpopulation recognition requires advanced techniques since the expression patterns of CSC-specific markers varied throughout cancer types. The foundation of isolation methods like as FACS and MACS is marker expression.

CSCs, through their adaptive processes, have therapeutic resistance. Some of the strategies involved include evasion of apoptosis, quiescence, DNA repair, reactive oxygen species regulation, efflux pumps, and microenvironmental support. Because of the high expression of the ATP-binding cassette transporter, CSCs strongly expel chemotherapeutic drugs [44-46]. Their quiescent status allows them to re-enter the cell cycle and evade treatment. CSCs utilize anti-apoptotic signaling pathways and antioxidant defences to maintain the levels of reactive oxygen species low. These features, which include resistance mechanisms, dynamic marker expression, and microenvironmental influence [47], make therapeutic targeting challenging. The answers include multi-target tactics, single-cell technologies, and targeting plasticity pathways. Cancer stem cell (CSC) treatments are prone to side effects and toxicity [48]. Common signalling pathways required for CSC development and survival might have unsuspected negative impacts. If the CSCs are not selective, then treatments involving CSCs can cause damage to the non-target tissues [49]. Because of their similar microenvironments, CSC-specific immunotherapies can potentially destroy stem cell niches in healthy tissues and cause adverse immunological responses [50]. Biomarker monitoring, combination treatment, targeted delivery systems, selective pathway modification, and marker refinement are examples of risk-reduction strategies [51]. Treatments that target CSCs must find a balance between safety and efficacy. To avoid immune recognition, CSCs use several strategies that include use of immunosuppressive drugs, low immunogenicity, strong expression of immune checkpoint molecules, changed antigen processing, and interaction with tumour microenvironments [52]. However, the practical implementation of anti-CSC drugs is challenged by limited preclinical models, resistance mechanisms, toxicity, off-target effects, barriers created by technology and regulation, and ethical and financial issues [53]. International collaboration, comprehensive preclinical and clinical research, cost-effective solutions, and ethical frameworks are required to guarantee equitable access and safe usage.

Potential uses of stem cell therapy in breast cancer: Possible regeneration of good tissue in the breast or surrounding tissues following treatments such as chemotherapy or radiation may occur with stem cells. It may help to improve post-treatment recovery and quality of life.

Targeting cancer stem cells: In a few breast cancers, there could be a minor population of cancer stem cells resistant to the current therapies. Investigators are now designing ways to selectively target and destroy these cells so that the occurrence of recurrence and metastasis would be minimized. It may also modify or eliminate cancer stem cells through the modulation of immunity or utilization of modified stem cells.

Improvement of immunity stem cells may also contribute to the improvement of immune response toward cancer. For example, stem cells might provide cells reactivated to efficiently and highly react towards the cancerous cells for their killing. Some researchers are even targeting the incorporation of stem cells into targeted therapy delivery directly to the cancer cells.

Preclinical studies and animal models

Understanding the behaviour of breast cancer cells and creating novel treatments for the disease are accomplished through stem cell research and preclinical animal models. These studies employ a range of animal models, such as non-human primates, pigs, rats, mice, and hamsters. Xenografts of human breast cancer cell lines growing in immunodeficient mice, chemically induced mouse models (such as 7,12-dimethylbenzanthracene, N-nitrosomethylurea), virally induced mouse models (such as mouse mammary tumour virus, polyomavirus), and genetically modified mouse models are among the animal models currently available for testing breast cancer medications [54]. The creation of molecularly targeted medications that might have more specificity or activity in breast cancer should be more appropriate for these models. However, the rate at which novel breast cancer medications are effectively transferred from the lab into clinical practice has not much improved despite the use of these models for nearly 20 years.

Tumour cells can be found and either killed or given drugs that destroy tumours via radiolabelled monoclonal antibodies without endangering healthy cells. It may be possible to replenish immune cells lost due to monoclonal antibody therapy, which kills tumour cells, with bone marrow or peripheral stem cell transplants. The purpose of this phase I trial is to determine whether bone marrow or peripheral stem cell transplantation, in conjunction with radiolabelled monoclonal antibody therapy, is an effective treatment for patients with metastatic breast cancer [55].

One clinical trial that uses therapeutic agents to target CSC in BC is the AVASTEM NCT01190345 trial, which assessed the anticancer potential of preoperative Bevacizumab, a monoclonal antibody that targets the vascular endothelial growth factor (VEGF) receptor, in conjunction with standard therapy in 75 BC patients. Following four treatment cycles, the percentage of cells that tested positive for the ALDH1 marker indicated the fraction of BCSCs. Since bevacizumab did not alter BCSC rates in comparison to normal neoadjuvant chemotherapy, this trial cannot validate the effect of the drug on breast CSC cells. As a result, the use of this antibody in the management of BC remains debatable [56].

The presence of the cancer stem cell biomarker CD44+/CD24− y ALDH1 was assessed as a predictor of response to trastuzumab in 1874 samples from BC patients who had previously received treatment in the NSABP-B-31 trial as part of the clinical trial NCT01424865. The CD44+/CD24− phenotype may be utilised to predict clinical outcome and responsiveness to Trastuzumab treatment in patients with HER2-positive primary BC, according to the results of this clinical trial [57].

In order to assess BCSC inhibitors preclinically, the Chang lab, working with Michael T. Lewis, created stable breast cancer-in-mice xenograft models. These types of models are created by transplanting human breast cancer tumour biopsies into the fat pad of the mammary gland of immune-deficient mice. The mice are given the medicines, and the tumour is then removed for thorough analysis in BCSC assays to see how well the stem cell targeted drugs change the tumorigenic BCSC population. Among these BCSC assays are: 1) flow cytometric measurement of aldehyde dehydrogenase activity (ALDH+ and CD44+/CD24−, respectively) and BCSC cell-surface markers 2) mammosphere forming efficiency (MSFE); and 3) re-transplantation to assess the presence of tumor-initiating cells (TICs) [58].

Cancer stem cell biomarker NCT00003042, assessed for the effectiveness of chemotherapy plus stem cell transplantation in treating patients with stage IIIB breast cancer is being investigated in this phase II experiment [59].

One antibiotic that has been found to be an effective anti-BCSC drug is salinomycin (SLM). SLM suppresses the formation of breast tumours *in vivo* and decreases the percentage of CSC by more than 100 times when compared to PTX. Additionally, by altering the WNT and Hh signalling pathways, it reduces the expression of genes linked to BCSC.As a novel treatment for TNBC, SLM has also been explored in combination with the histone deacetylase inhibitor LBH589 (Panobinostat). Through the induction of apoptosis, cell cycle arrest, and EMT regulation, the combination administration of these medications demonstrated an efficient and synergistic reduction of tumour growth in an ALDH1+ TNBC xenograft mice model, with no discernible severe toxicity [60].

According to a recent study, SLM and its C20-propargylamine derivative (Ironomycin 2) cause ROS generation, which kills BCSCs once iron builds up in lysosomes. In order to target BCSC cells that overexpress the CD44 receptor, Muntimadugu., *et al*. created another delivery strategy for SLM. They made nanoparticles loaded with SLM or PTX and coated them with hyaluronic acid. According to the study's findings, bulk tumour cells and CD44+ BCSCs were both eradicated. A promising strategy to combat cancer recurrence caused by resistant BCSCs is combination therapy using PTX nanoparticles and HA-coated SLM nanoparticles.

Ethical and safety concerns

The ethical and safety concerns with regard to stem cell therapy for breast cancer include: tumorigenicity, referring to the proliferation of cancerous cells from the stem cells themselves; lack of long-term follow-up data related to safety and efficacy; types of stem cells utilized, being embryonic vs adult; and potential immunologic responses. Above all, they demand strict clinical trials to be carried out, thereby ensuring complete patient safety along with ethical treatments. Particularly important in this context is whether the therapy of stem cells would inadvertently induce tumour growth instead of controlling it.

Ethical issues

Use of embryonic stem cells

Some people have ethical reservations about using embryonic stem cells because the harvesting process could harm human embryos.

Patient consent

Before agreeing to treatment, patients must be fully informed about the possible dangers and advantages of stem cell therapy, as well as the experimental nature and associated uncertainty.

Access to treatment

The most comprehensive study conducted so far has identified two primary risks involved with stem cell-based therapy, which are tumorigenicity and immunological reactions. Both these risks are dependent on the nature of the stem cells and are also extrinsic in nature. Considering all this, the fast-emerging field of stem cell therapy needs to focus more on the development of a comprehensive risk evaluation of the technologies and on establishing methodical follow-up monitoring of post-transplantation results. Clinical stem cell therapies are not immune to several risk factors, both extrinsic and internal. The special focus of stem cell ethics has always been the development and therapeutic application of hESCs. Current ethical debates around stem cell-based therapy centre on the potential for infinite differentiation of iPSCs, which can be utilised in human cloning, as well as the potential for the creation of human embryos and human-animal chimaeras.

ASCT (Autologous stem cell transplant) is a possibly curative therapy option for breast cancer, which is a potentially fatal disease, both locally progressed and metastatic. A woman receives a transfusion of her own stem cells, which were isolated before to the start of high-

dose chemotherapy, just after the treatment. ASCT replaces the lost bone marrow since high-dose chemotherapy not only kills tumour cells but also essential haematopoietic stem cells. Extending a patient's overall survival or disease-free survival may be beneficial, but it comes with serious side effects such infections, haemorrhage, secondary cancers, infertility, and even the possibility of therapy-induced death.

Factors unique to stem cell treatment for breast cancer: Since breast cancer stem cells (BCSCs) are frequently resistant to traditional treatments, identifying and precisely targeting these cells is essential to preventing tumour recurrence and for Tumour growth monitoring, to identify any indications of tumour recurrence or new tumour development, patients must be closely monitored after treatment.

Future Directions and Perspectives

The use of stem cells to treat breast cancer has a promising future. New and creative approaches to using stem cells to treat this illness are being developed by researchers as they gain more knowledge about them.

The following are some potential future paths for breast cancer stem cell therapy: Creating novel and more efficient methods for breast stem cell delivery, novel methods for producing new breast tissue using stem cells, novel approaches to target and eliminate cancer cells using stem cells. Genetic modification of the MSCs may result in an overexpression of advantageous genes, such as suicide genes (which cause cancer cells to undergo death) or cytokines (which stimulate immune systems). Numerous attempts have been made to use MSCs to deliver anticancer medicines to tumours because of their strong capacity to target tumour locations. In this sense, MSCs transported oncolytic viruses, such as DOX, to the tumour site, where they subsequently halted tumour growth and triggered apoptosis. Cell-cell contacts and associated EVs allowed MSCs to perform their role. It has been demonstrated that EVs derived from native MSCs play a dual role in cancer treatment, just as native MSCs.

Conclusion

Stem cell therapy holds great promise in terms of novel strategies for early diagnosis and individualized therapeutics in breast cancer management. According to recent studies, the very potential of stem cells supports our understanding of the initiation of cancer, metastasis, and the development of resistance to conventional therapies. While stem cell-based therapy in breast cancer is still at its infancy, advances in gene editing, stem cell biology, and personalized medicine allow the hope for better therapies. However, issues remain to be resolved; these include stem cell delivery pathways with more promise for safety application and low tumorigenicity risk, along with ethical issues. Future studies and clinical trials would have to confirm the efficacy and safety of stem cell therapy in breast cancer, thus possibly improving patient outcome.

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