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Review

# Stem Cell Therapy in Cancer

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**ABSTRACT**

Cancer is a widespread collection of diseases responsible for millions of deaths annually. Various approaches have been employed in its treatment, including chemotherapy, radiotherapy, and surgical interventions. In recent years, there has been growing interest in the potential of stem cells for cancer therapy. Stem cells possess unique properties, such as self-renewal and differentiation capabilities, which make them valuable in various medical applications. Different types of stem cells, including embryonic stem cells, adult stem cells, and induced pluripotent stem cells, have been investigated for their potential use in cancer treatment. Stem cell-based therapies offer several potential advantages in cancer treatment. They can differentiate into specific cell types, which may allow for the regeneration of damaged tissues and organs caused by cancer or its treatment. Stem cells can also serve as delivery vehicles for targeted therapies, enabling the precise delivery of therapeutic agents to tumor sites. Additionally, they can modulate the immune system and have the potential to stimulate anti-tumor immune responses. However, it is crucial to understand and monitor the potential side effects associated with these treatments. Ongoing research and clinical trials aim to further refine stem cell therapies and improve their safety and efficacy for the benefit of cancer patients worldwide. This chapter provides a general overview of cancer, the application of stem cells in treatment, and the potential side effects associated with this therapeutic modality.

**Keywords:** Cancer, embryonic stem cells, pluripotent stem cells, stem cell therapy.

Cancer is a perilous illness responsible for millions of annual fatalities, and despite advancements in diagnosis and treatment, the reduction in mortality rates remains minimal. The extensive understanding of cancer genetics acquired during this period will enable scientists to develop more comprehensive therapeutic approaches.[1]

Depending on the type of cancer and its progression, the type of treatment and the process followed are different. Surgery is among the first options. It is used for the direct removal of solid tumors in an area. The other option is radiotherapy. It kills tumors by damaging cancer cell deoxyribonucleic acid (DNA). Another method is chemotherapy. In chemotherapy, tumor growth is slowed or stopped by using drugs with a high toxicity rate. Immunotherapy involves the use of monoclonal antibodies, checkpoint inhibitors, cancer vaccines, and acquired cell transfer. With significantly improved clinical outcomes, it is becoming an important healer for cancer.[2]

Immunotherapy involves the use of monoclonal antibodies, checkpoint inhibitors, cancer vaccines, and acquired cell transfer. With significantly improved clinical outcomes, it is becoming an important healer for cancer. In addition, the disadvantages of current treatments cause suboptimal effectiveness, treatment resistance, and tumor recurrence. In addition, many phenomena related to the off-target effects of therapeutic drugs and immune responses are observed.[3]

In addition to the treatments we have mentioned; Stem cell therapy, which uses stem cells and includes all procedures, provides an important option in the fight against cancer. Due to its enhanced target on tumor cells, it increases the therapeutic efficacy of other treatments. In this way, off-target incidents are

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reduced. Numerous stem cell-assisted strategies are currently being investigated in preclinical trials. It shows both major advances and challenges in cancer treatment. Therefore, more evaluation is needed.[4,5]

In this chapter, an overview will be provided regarding both the types of stem cells and the underlying mechanisms of action of stem cells in cancer treatment. Additionally, the side effects that may occur in this treatment, as well as current treatments, will be discussed.

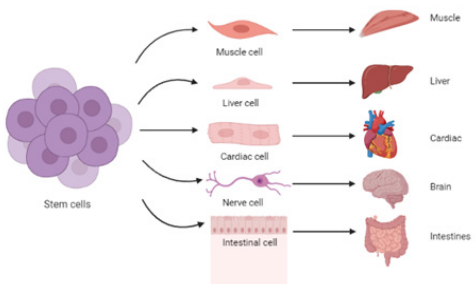


Figure 1: The differentiation of stem cells leads to the formation of various tissues and organs.

## STEM CELLS IN CANCER TREATMENT

Different types of stem cells exhibit different proliferation, migration, and differentiation capacities in anti-tumor treatment.

### Pluripotent Stem Cells

Embryonic stem cells (ESCs) isolated from the undifferentiated cells of the embryo have the ability to develop into all kinds of cells except those found in the placenta. However, the applications of ESCs for clinical trials are restricted due to ethical considerations. In 2006, the induction of pluripotent stem cells (PSCs) from somatic cells made a major breakthrough in cell biology. These PSCs are; while eliminating the ethical issues arising from embryo destruction, share the same characteristics as ESCs. So far, both ESCs and PSCs have been of great importance for the induction of effector T- and NK cells and for the production of the anti-cancer vaccines that will be mentioned.[6-8]

Pluripotent stem cells, which have an unlimited capacity for self-renewal and the potential to form all cell types in the body, have many similarities with cancer stem cells (CSCs). The PSCs, which have an unlimited capacity for self-renewal and the potential to form all cell types in the body, have many similarities with CSCs. They are usually derived from early embryos directly through ESCs or from the reprogramming of somatic cells. These cells have been used as promising sources for cell-based treatments in clinical trials related to spinal cord injuries, diabetes, and age-related macular degeneration treatment. However, PSC-based cancer treatment studies are essentially limited to the derivation of functional cancer-fighting cells containing dendritic cells and lymphocytes derived from PSC and are transplantable cells such as hematopoietic stem cells (HSCs).[9,10]

The results of some studies have shown that exposure to the PSC microenvironment of different types of cancer cells can inhibit nodal expression and suppress the malignant properties of these cells. The importance of these PSC-based research priorities points to a new vaccination strategy against CSCs, which could possibly induce long-term memory against a broad spectrum of tumors.[11]

### Adult Stem Cells

Adult stem cells (ASCs) develop into many specialized cell types of tissue and organ. This group includes hematopoietic stem cells, mesenchymal stem cells (MSCs), and neural stem cells (NSCs). These cells are often used in cancer treatment. Hematopoietic stem cells found in the bone marrow are able to form all the blood cells present in the body. Until now, HSCs derived from cord blood have been a stem cell procedure approved by the Food and Drug Administration to treat multiple myeloma, leukemia, and certain blood system disorders.[12]

Mesenchymal stem cells are found in many tissues and organs. Tissue repair and regeneration play a big role. Adipocytes, chondrocytes, and osteocytes multiply *in vitro* and can produce a variety of cell types. They have different biological properties and are widely used to support other treatments or to offer therapeutic agents in the treatment of various cancers.[13] The NSCs, which are initially located in the central nervous system, are able to self-regenerate. It is able to produce new neurons and glial cells. These cells are widely studied to treat both primary and metastatic breast, lung, and prostate cancers.[14]

### Cancer Stem Cells

With the deepening of tumor biology research, clinical diagnosis, and cancer treatment have improved significantly in recent years. However, the high recurrence rate and high mortality rate are still unresolved and are closely related to the biological properties of CSCs. With a better understanding

of CSC properties, research on tumor biology has entered a new era. Therefore, understanding the biological properties of CSCs is of great importance in the diagnosis and treatment of tumors.[15]

The survival of patients with cancer has improved significantly, primarily due to multidisciplinary care, improved chemotherapeutic agents in both adjuvant and metastatic settings, the introduction of targeted biological agents, and the inclusion of palliative care services in the management scheme. However, a significant number of patients continue to experience relapses after adjuvant treatment, and the survival associated with stage IV solid tumors is still low. A primary or acquired resistance to chemotherapeutic and biological agents is responsible for the failure of many agents used to treat patients with malignancy. This can be explained by the presence of intra-tumor heterogeneity and the molecular complexity of many cancers.[16]

Cancer stem cells have been identified in a number of solid tumors, including breast cancer, brain tumors, lung cancer, colon cancer, and melanoma. They have the capacity to self-renew, create generations different from themselves, and take advantage of common signaling pathways. The CSCs may be the source of all tumor cells found in a malignant tumor, the cause of resistance to the chemotherapeutic agent used to treat the malignant tumor, and the source of cells that cause distant metastases.[17]

Cancer stem cells, tumor cells, or immature progenitors of tumor-initiating cells are produced by epigenetic mutations in normal stem cells or precursor cells. These cells are found in tumor tissues. It plays an important role in cancer growth, metastasis, and recurrence. Targeting CSCs in the treatment of different solid tumors offers promising potential.[18]

**Possible Applications of Stem Cell Therapy in Cancer Treatment**

Various strategies have been developed in the treatment of cancer. These are in general terms; HSC transplantation is involved as MSC infusion for post-cancer treatment, stem cells developed for therapeutic carriers, and vaccine production.[19]

**Hematopoietic Stem Cell Transplantation**

The exploration of HSC transplantation in human studies began in the 1950s. This research was inspired by observations in mouse models, which indicated that introducing healthy bone marrow components into bone marrow experiencing myelosuppression could enhance receptor function. These animal-based studies soon found their clinical application in humans when the first successful bone marrow transplant in monozygotic twins was performed in a patient with acute leukemia in New York City in 1957. As a result, the doctor who performed the procedure, Dr. Thomas continued his research on the development of bone marrow transplantation and later received the Nobel Prize in Physiology and Medicine for his work.[20,21]

Hematopoietic stem cell transplantation is a preferred treatment for a variety of ill-progressing and non-progressive diseases in children and adults. Originally developed as a kind of salvage treatment after correcting serious deficiencies in the hematopoietic system as well as high-dose chemotherapy and radiation for cancer patients, this treatment method has been transformed into an immune treatment adopted for various malignancies and autoimmune diseases. The procedure has helped to obtain important information about the bone marrow environment, the biology of hematopoietic stem cells, and tissue compatibility. The development of this new discipline has allowed numerous groups working around the world to treat diseases previously thought to be fatal.[22]

After undergoing high-dose radiotherapy or chemotherapy procedures, patients with multiple myeloma, leukemia, and lymphomas have received HSC transplantation as a treatment modality. In addition, this procedure is currently used in combination with chemotherapy or immunotherapy, and research is underway to treat other types of cancer, such as brain tumors, neuroblastoma, sarcomas, and breast cancer.[23]

**Mesenchymal Stem Cell Transplantation**

Mesenchymal stem cells were first described by Friedenstein and colleagues in 1970 as spindle-bone marrow stromal cells. Four years later, they discovered that MSCs could form colonies outside the body that stick to the wall like fibroblasts. Therefore MSCs are also known as colony-forming unit fibroblasts (CFU-Fs). In 1991, Caplan coined the term "mesenchymal stem cells" and predicted that these mesodermal-derived cells would represent the main arsenal of autologous therapies for regenerative purposes. With the advancements that have emerged in recent years, MSCs have become the most studied stem cell population. They are widely used in clinical trials and in the treatment of various diseases, especially neurological diseases.[24,25]

Mesenchymal stem cells have been isolated from the bone marrow for the first time. They have

previously been used in the lung, liver, kidney, placenta, fallopian tubes, endometrial polyps, adipose tissue, tooth extract, salivary glands, lower cone, umbilical cord blood is isolated from various tissues such as menstrual blood, and other tissues. It can refer to mesenchymal markers including CD90, CD105, CD73, and others, but cannot refer to CD11b, CD14, CD19, CD34, CD45, and human leukocyte antigen (HLA)-DR. The harvesting of MSCs from various tissues can be influenced by different donor characteristics, which in turn affect the surface markers, quality, and quantity of the isolated MSCs. Currently, the most commonly reported sources of MSCs used in clinical trials are bone marrow, adipose tissue, and umbilical cord. Stem cells derived from adipose tissue (AD-MSCs) have been found to exhibit the expression of CD49d and demonstrate a higher capacity for producing hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) compared to stem cells derived from bone marrow-derived MSCs (BM-MSCs).[26,27]

Invasive tumor removal or aggressive tumor treatment may usually cause damage to normal tissues and the hematopoietic system. The evidence shown is that MSC infusion helps in maintaining an undifferentiated state and proliferation in HSC and increases the outcome of the treatment administered. In addition, recent clinical trials have shown promising results with no side effects when MSC and HSC are transplanted together. Apart from this information, it is stated that MSCs provide body tolerance to high doses of chemotherapy and in the healing of injured organs.[28,29]

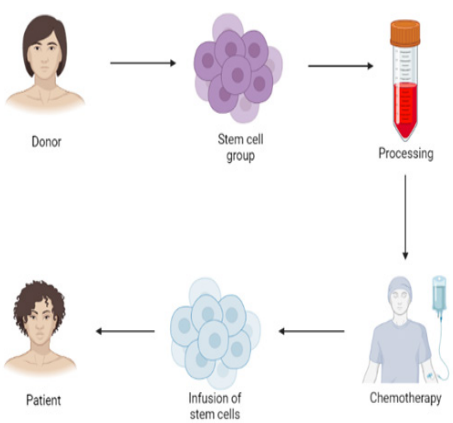


Figure 2: Initially, the donor's stem cells undergo processing before being infused into the cancer patient undergoing chemotherapy, thereby facilitating the occurrence of stem cell transplantation.

**Stem Cells Acting as Potential Therapeutic Carriers**

The reason for using carriers are: they protect therapeutic agents from rapid biological degradation, reduce the side effects of the system and increase local therapeutic levels due to the intrinsic tumor-targeting effect of stem cells. The effectiveness of the system depends on the number of localized stem cells.[30]

Similar to normal tissue, many tumors have a hierarchical organization in which tumorigenic CSCs differentiate into non-tumorigenic progeny. Some studies have shown that although CSCs and non-tumorigenic progeny within the same clone may share common genotypes, they show different epigenetic profiles resulting in changes in multiple signaling pathways. Many of these pathways provide cell adaptation to microenvironmental stresses, including inflammation, hypoxia, low pH, nutrient deficiency, and cancer-prevention treatments.[31]

**Stem Cell-Derived Anti-Cancer Vaccines**

So far, three well-known types of cancer treatments have been developed. These treatments are called surgery, chemotherapy, and radiotherapy. They either destroy cancer cells or attack them directly. These treatments treat cancer at an earlier stage but are often ineffective to treat cancer at advanced or recurring stages. Basic and clinical research on the tumor microenvironment, which consists of cancerous, stromal, and immune cells, demonstrates the critical role of anti-tumor immunity in cancer development and progression. Cancer immunotherapy has been proposed as the fourth cancer treatment.[32]

The clinical application of immune checkpoint inhibitors, particularly anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) and anti-programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) antibodies, in various types of cancer, represents a major breakthrough in cancer treatment. Still, data on immune checkpoint inhibitors suggest that these are not always effective, but only effective in limited cancer populations.[33]

Treatments that target CSCs greatly increase therapeutic efficacy in the treatment of cancer. In particular, the production of these vaccines shows high performance. In studies conducted so far, some difficulties still arise, despite the rapid advancement of CSC, which has been isolated from tumor tissue.[34]

## SIDE EFFECTS AND POTENTIAL RISKS OF STEM CELL THERAPY

### Tumorigenesis

With normal stem cells, CSCs share basic biological signaling pathways. If the environment of stem cells changes negatively, normal stem cells turn into CSCs, and then tumor tissue is formed. In addition, stem cells that are exposed to external conditions during culture before transplantation and transplanted change their genomic expression and subsequent phenotype. The longer the culture time, the more likely it is that stem cells will turn into cancer cells. For example, it has been shown that approximately 50% of MSCs turn into malignant cells on their own after one month of being in culture.[35,36]

### Transplantation

Hematopoietic stem cell transplantation is becoming an effective practice in the treatment of hematological and lymphoid cancers. In addition, tissue or organ dysfunction, infections associated with the immune response that does not progress normally, recurrence, and secondary cancers cause long-term side effects in patients, including patient quality of life.[37,38]

### Drug Toxicity and Drug Resistance

The number of cells localized within the tumor affects the effectiveness of stem cells in using them as gene and drug carriers. In the studies conducted, it has been stated that approximately 5% of the total number of stem cells can be placed in the tumor tissue after systemic injections and remain stable during this placement process. Cells injected intravenously are initially found in lung tissue, then progress to the spleen, liver, and lymph nodes, and are finally cleared from the body. This situation brings some problems. First of all, the levels of therapeutic agents that have not yet been targeted are high to induce toxicity to normal tissues and organs. Subsequently, insufficient drug levels in the tumor tissues only reduce the effectiveness of the treatment applied and increase the effectiveness of drug resistance.[39,40]

### Viral Infections

Viral Infections are a common and effective method of modifying stem cells for the gene carriers used. The main problems that arise in this method are strong viral immunogenicity, which will cause adverse immune responses, cause toxin release, elimination of transductive cells, limited transgenic capacity size, and death. Therefore, viral vectors; When specifying targeted sequences for effect in the anti-cancer process, specific sequences involved in naturally occurring toxicity in cancer patients need to be carefully modified to delete them.[41]

In conclusion, cancer continues to be a serious disease that affects human life from past to present. In the process of cancer treatment, procedures such as surgical procedures, chemotherapy, or radiotherapy are applied. In addition, the immunotherapy method is also used. In recent studies, stem cells have also come to an important place in cancer treatment. The various stem cells used play a role in the treatment process of many cancers in different ways. However, while performing these procedures, different side effects occur in cancer patients. This sometimes causes tissue-organ numbness and sometimes high toxicity. Therefore, stem cell studies should continue to be investigated in more detail. As the studies continue, these side effects will decrease and stem cells will become more prominent in the coming years.

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