Molecular Biology of Stem Cell Therapeutics in Cancer Treatment: Underlying Potential Applications

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Abstract

Numerous populations of tumor cells that may survive, develop, and proliferate under specific circumstances make up cancer. Resistance to treatments and cancer recurrence might result from the often insufficient and nonspecific target therapy. The scientific study of stem cells was recognized as a viable approach to creating more potent anti-cancer drugs in the last few years. Regeneration, migration toward tumor locations, differentiation into many cell types, and modulation of adjacent cells are some of the amazing properties of stem cells. These abilities can be used in regenerative medicine, targeted medication administration and even the production of immune cells to combat cancer. This chapter has examined the molecular processes in connection with the application of several types of stem cells to cancer treatment, with an emphasis on how they could enhance treatment results, current advancements in medical or therapeutic applications, such as immunological modulation.

Keywords: Cancer treatment, Stem cell biology, Mechanisms, Potential Applications, Therapeutics

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Introduction

Scientists have pointed out that stem cells have provided substantial insights into morphological, developmental as well as physiological aspects of 'stem cell niche' its generation, support as well as tissue and organ repair potentiality in situations of damages. Because they may be able to promote the multipotent differentiation of stem cells, both in vivo and ex vivo into functional offspring that could assist mankind in repairing its defective tissues and organs, recent advancements in the stem cell biology are quite popular and holds significant therapeutic value (Siegel et al., 2016). The concept of an adult stem cell as a slowly dividing cell that is capable of differentiating into various mature cell types is relatively recent: the idea of a stem-cell 'lineage' is also novel – but compelling given that, for the most part, the multipotent adult stem cells are present in most tissues as well as organs of the body. These are stem cells derived from amniotic membrane, embryos, fetal tissue, and the UC. These include gastrointestinal system, pancreas, kidneys, lungs, liver, adipose tissues, muscle tissue, skin, eyes, bone marrow (BM), brain, heart, ovaries, prostate, breast, and testes (Vanneman & Dranoff, 2012).

Therapists may be able to tailor out more effective therapy regimens if they have a primarily understanding of cancer biochemistry. The treatment strategy depends on the kind and grade of cancer and goal of treatment. The first method of direct excision of solid tumors in one region is the surgical. The therapy can help to get rid of tumors by destroying the DNA of cancer cells. Chemotherapy utilizes very poisonous drugs to arrest or slow down growth of cases (Arnold et al., 2020). Immunotherapy, which encompasses adoptive cell transfer, checkpoint inhibitors, monoclonal antibodies, and cancer vaccines, has become a major cancer treatment with much improved clinical outcomes (Young et al., 2018). Nevertheless, the major limitations associated with current treatments include inability of current therapies to accurately identify and home in on tumor areas other than effector CAR cells; hence, present low efficacy, therapy resistance, and lead to tumor relapse (Cui et al., 2021).

In the meanwhile, the perspective in fight against cancer is stem cell treatment, which means all the treatment methods using stem cells. Due to that, it may enhance the efficiency of other drugs affecting tumors and reduce side effects (Zhang et al., 2017). Preclinical studies are now being conducted on a number of stem cell-based approaches, which present both significant opportunities and difficulties for cancer therapy (Zhou et al., 2021). Thus, it is necessary to evaluate more results to check their relevance for the further clinical study. The goals of this work are to introduce various forms of stem cells and discuss how they work to destroy cancer cells. We will also give you an update on recent advancements and the negative effects of this treatment. Additionally, this study will offer broad suggestions for the future.

Types of Stem Cells for Cancer Treatment

Stemness in anti-tumor therapy depends on different abilities depending on the stem cells' ability to move, to differentiate or replicate.

Pluripotent Stem Cells (PSCs)

ESCs, which are taken from inner cell mass of embryo is capable of developing all the variety of cells other than those forming the placenta. But there does not seem to be a vast use of ESC in clinical research due to ethical concerns. The discovery of Yamanaka factors in 2006 to create pluripotent stem cells from somatic cells in lab culture grew to become a primary development of cytology (Timmermans et al., 2009; Knorr et al., 2013). Like ESCs, these iPSCs resolve the ethical conundrum of destroying embryos. These days, HESCs and iPSCs are both useful tools for producing effector T- as well as NK cells and developing anti-cancer vaccines (Ouyang et al., 2019).

Adult Stem Cells (ASCs)

ASCs have the potentials capacity to differentiate into a variety of specific tissue and organ cell lineages. These cells that are mostly used in treatment of cancer include hematopoietic stem cells (HSCs), neural stem cells (NSCs), and MSCs. HSCs are mainly in bone marrow and are capable of producing all the body's adult blood cells. At the time of writing, the FDA has only certified that HSCs from cord blood can be used as stem cell therapies in disorders of the blood system, leukemia; multiple myeloma (Copelan, 2006). MSCs are particularly important in terms of tissue repair and regenerative medicine, and may be located in many different tissue types and organs of the body. They may exhibit exponential growth in vitro and differentiate into distinct cell kinds including osteoblasts, adipocytes as well as chondrocytes. Due to specific bio-and-immunological characteristics, MSCs have been employed to solve various tumor indications by transferring curative substances or as supporting injections (Christodoulou et al., 2018; Lin et al., 2019). Apparently originating from the brain and nervous system, NSCs are capable of autonomic proliferation and differentiation into glial and neurons (Kanojia et al., 2015).

Cancer Stem Cells (CSCs)

Regular stem cells and precursor cells can be transformed into cancer stem cells (also called tumor-initiating cells, cancer stem cells, or stem-like cells) by epigenetic modification. They often located in the tumor tissue; hence they are responsible for tumor growth, spreading and relapse. Consequently, focusing on CSCs might have the potential to treat numerous solid cancer kinds (Samadani et al., 2020). By concentrating on CSCs, scientists hope to develop more effective treatments that not only shrink tumors but also eliminate the root cause of metastasis and recurrence, offering a possible approach to treating many solid tumor types (Chang, 2016).

Mechanisms Underlying the Action of Stem Cells in Cancer

Stem Cell Homing and Integration in Cancer Treatment

When malignant tumors are treated with extremely high doses of chemotherapy to kill every cancer cell, leukocytes and blood-forming cells are either totally or partially killed. Some patients require intravenous injections of autologous or allogeneic HSCs at some point. Through a mechanism known as homing, these HSCs are believed to swiftly move into certain bone marrow (BM) stem cell niches. When the transplanted HSCs come into contact with BM, they undergo the engraftment process, which leads to the development of specialized blood cells (Chatterjee et al., 2021). The principal molecular means underlying the HSC homing process, the direct binding of the gradient SDF-1 created by the BM SCNs cells to the stem cell CXCR4 receptor. Extracellular ATP or UTP, ceramide-1 phosphate, sphingosine-1 phosphate, Ca2+, and H+ ions are additional molecular signaling molecules (SEITZ et al., 2005; Juarez et al., 2012). Moreover, HSCs need to interact with the endothelium through VLA-4/5, LFA-1, CD44, and the synthesis of the extrinsic matrix-degradable enzyme MMP-2/29 in order to move through blood arteries (Wang et al., 2023).

Stem Cells in Tumor Growth and Migration

Numerous cell types move led to the tumor microenvironment, which is defined by an accumulation of extracellular matrix (ECM) along with secreted paracrine substances. These cell types include endothelial cells, infiltrating immune cells, and MSCs. Because of their persistent oxidative stress, inflammation, and hypoxia, tumors are viewed as chronic wounded tissue that never heals. It is thus postulated that MSC migration to ischemia or injured areas as similar to MSC delivery into the tumor milieu. Actually, by secreting various chemoattractant substances, tumor cells and immune cells linked to malignancy can aid in this process (Pattabiraman & Weinberg, 2014). MSC migration into the tumor microenvironment is facilitated by the secretion of SDF-1, CCL-25, CXCL16, and IL-6 by osteosarcoma, myeloma multiplex, breast cancer, and prostate cancer cells, for instance (Sun et al., 2014; Jiang et al., 2019). Immune cells that are present in the tumor via secreting cytokines that favors inflammation including IL-1β and TNF-α which in return attracts MSC inside the tumor and also prompts their differentiation. At the tumor site MSCs differentiate into myofibroblasts or endothelial cells that play a role in growth of tumor stroma (Sullivan et al., 2014).

Signaling Pathways in Cancer Stem Cells (CSCs)

Several key pathways involved in CSC function:

- Wnt/β-catenin pathway
- Notch signaling
- Hedgehog signaling
- PI3K/Akt/mTOR pathway
- TGF-β signaling

Some of the molecular pathways which regulate regular growth of stem cells include these pathways. The constant alterations of those signaling processes will give rise to CSCs and then, cancer cells. Due to the relative high capacity for self-renewal, differentiation, CSC is

beneficial for growth, recurrence and metastases of tumor. These cells may also be the reason why the cancers are so invulnerable to normal treatments. Hence, understanding of the properties of CIKSCs is crucial to achieving the goal of finding a perfect cancer treatment (Matsui, 2016; Batlle & Clevers, 2017).

Some of the tumor types in which CSCs have been identified include cancers of the gastrointestinal tract, leukemia, brain, breast, and lungs. They are single and characterized by techniques like metabolic/functional profiles, and surface proteins. CSCs exhibit similar features and functions of normal stem cells from which they are originated. However, some of the specific surface markers which are used to identify CSCs originate from highly dissimilar cancers including; CD133 (HSC marker), CD44, Lgr5, CD24 and EpCAM (Yang et al., 2020; Zhou et al., 2021). Furthermore, CSCs that has low proliferation rate, high glycolytic activity, immune tolerance and therapy resistance. Oncofetal and cancer/testis antigens are TAA which are normally produced only during germ cell differentiation throughout the embryonic development are some of the CSC specific immune TARAs that can be targeted for immunotherapy.

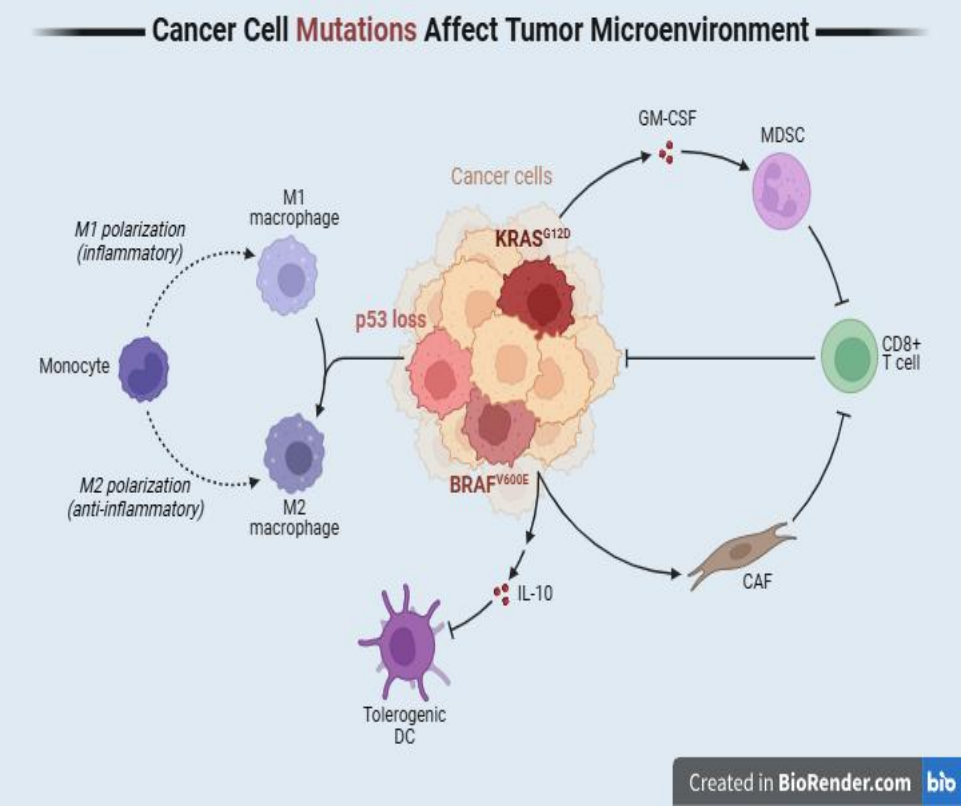

Fig. 1: Tumor Formation and its Complex Microenvironment

CSCs are generated when normal stem cells or precursor/progenitor cells have an epigenetic change (Figure 1). These cells play important function of stemness, initiation of tumor, their maintenance and also metastasis. Cancer associated immune cells such as T-cell, Macrophages (MΦ), Dendritic cell (DC), Cancer associated Fibroblasts (CAF) are present in the tumor niche but tumor cells and SCs. In addition, all of those cells secrete chemo attractant factors (CXCL16, SDF-1, CCL-25, IL-6, TNF-a & IL–1 β) which are involved towards the migration of MSCs towards the tumor cells and these all are involved in tumor progression.

The Potential Applications of Stem Cell Therapy in Cancer

Numerous approaches, including immunological effector cell synthesis, MSC injection for post-cancer treatment, HSC transplantation, stem cells as treatment vehicles, and cell vaccines, have been used to treat cancer using stem cell therapy.

HSC Transplantation

HSC transplantation, a routine treatment for leukemia, multiple myeloma and lymphomas following cycles of extreme intensity radiation and chemotherapeutic intervention. Furthermore, this procedure is currently being studied more actively in clinical trials for many cancer types when combined with immunotherapy or chemotherapy like the brain tumor, neuroblastoma, sarcoma, and breast cancer (Casper et al., 2010; Cieri et al., 2021).

MSC Transplantation after Cancer Treatment

Regular tissue injury and injury to the hematopoietic system often arise by intense cancer treatment involving tumor excision and doses of the treatment. There is convincing evidence that the infusion of MSCs improves the overall treatment result by preserving the indeterminate state and proliferation of HSCs. Moreover, in patients who suffer from refractory GVHD, the MSCs with immunosuppressive properties may indeed treat the fast and intensive immune reactivity. Co-transplanting MSCs and HSCs has produced encouraging results in recent clinical trials with no associated side effects (Méndez-Ferrer et al., 2010). Steroid-resistant GVHD adult patients are still receiving MSC derived from

mesenchymoangioblast through multi-center to determine the safety, tolerance and efficacy of MSC infusion. Furthermore, there are indications that MSCs can hasten the repair of injured tissues and organs and may even improve on the body's capability to withstand high dose chemotherapy as a means of increasing the effect of this nontoxic agent on tumors (Lan et al., 2021).

Stem Cells as Potential Therapeutic Carriers

The use of stem cell in cancer treatment is justified by the following reasons: For therapeutic molecules, some of their proposed advantages included:

(i) Protection from rapid biological degradation

(ii) Reduction in incidence of systemic toxicity

(iii) Elevation of local therapeutic concentration due to inherent tumor tropism of stem cells.

The quantity of stem cells in the tumor's microenvironment determines how well this system fights tumors.

Genetically Modified Stem Cells

In order to increase the production and release of soluble factors such as prodrug-converting enzymes, chemokines, or tumor-toxic cytokines, this technique relies on the direct viral transduction of stem cells, including MSCs and NSCs. The former approach is commonly referred to as suicide gene therapy. Furthermore, they have persistent stem cells and may generate enzymes that change inert substances or prodrugs into active molecules that are even harmful to cancer cells (Chu et al., 2020). Furthermore, stem cells have the genetic capacity to create secretable cytokines and chemokines. TRAIL has a limited half-life because of the tumor-toxic TNF-α-related ligands that cause apoptosis after systemic delivery. Surprisingly, research has demonstrated that NSCs, which act as a gene courier that continuously regenerates TRAIL, can slow the progress of brain tumors and improve treated mice's life (Lan et al., 2021).

Nanoparticles (NPs)-Carrying Stem Cells

For a long time, NPs have been used to transport anti-cancer medications. The primary disadvantages are their unregulated absorption by normal cells, lack of targeted action, and quick elimination from the body. The ability of stem cells to easily transport NPs to tumor locations is intriguing. With this method, NPs may be absorbed into the cytoplasm or attached to the cell membrane's outer surface. Depending on their size, concentration, nature of the surface, and incubation time, NPs can be swallowed by active endocytosis or passive absorption. The two main issues are possible toxicity to the cell carrier and drug loading (Ertas et al., 2021). Additionally, stem cells can aid in tissue repair and regeneration, particularly after cancer treatments. Because autologous stem cells—those generated by the patient's personal body—reduce the risk of immunological disapproval, this approach is more customized and effective (Lin et al., 2023). The use of stem cells and nanoparticles shows enormous potential for developing more accurate, targeted cancer therapies with fewer side effects, however research and clinical trials are still ongoing. However, before this technology is used in clinical settings, issues like maximizing the makeup of nanoparticles and guaranteeing their effective loading with therapeutic compounds need to be resolved (Rosenblum et al., 2018).

Stem Cells as Carriers for Oncolytic Viruses (OVs)

These molecules increase in particular cancer cell, particularly over yielding vesicles (OVs). There is still the belief that in response to the OVs, tumor cell lysis occurs and that subsequent warning signals alert the immune system for enhanced control of malignant cells. While naked OVs can easily be identified and expelled from the body by the immune system. The stem cells might be presented as potential OV delivery and tumor-area safeguard vehicles. Similarly, MSCs were shown as efficient for loading attenuated oncolytic HSV and oncolytic OMV, and thus, the animals develop hepatocellular carcinoma and GBM (Marelli et al., 2018; Ghasemi Darestani et al., 2023).

Stem Cell-Derived Exosomes as Therapeutic Carriers

Exosomes have been used to contain a variety of cancer-fighting medicinal materials, including proteins, miRNAs, and small compounds. When compared to other manufactured nanoparticulates, these natural carriers provide a number of benefits, such as a higher loading capacity for the payload, improved internalization into tumor cells, and more stable and reasonably biocompatible nanoparticles. Additionally, it may be easily altered by adding certain proteins or ligands to the surface to improve the tumor microenvironment targeting effectiveness (Sun et al., 2021). Exosome loading of stem cell-derived anti-tumor mRNAs or siRNAs has been achieved, as in a traditional transfection method. For instance, exosomes released by marrow stromal cells containing miR-146b were recovered by Katakowski et al. In a rat model of a primary brain tumor, research found that injecting these exosomes directly into tumors inhibited the development of glioma xenografts. In a different study, exosomes released by MSCs that expressed miR-122 markedly increased the drug's anticancer activity on a model of hepatocellular carcinoma. Similarly, bladder cancer cells' polo-like kinase 1 gene was successfully silenced by siRNA mediated by MSC-derived exosomes (Wang et al., 2017; Burgos-Ravanal et al., 2021). There are two ways to load small molecule medications into exosomes: The first is that the human pancreatic cancer cell line's ability to proliferate was significantly suppressed by the exosomes of MSCs primed with paclitaxel. The study also showed that stem cells have the ability to absorb extracellular materials, load them onto exosomes, and then release them into the culture medium through the process of exocytosis (Lou et al., 2015; Zhang et al., 2022).

Stem Cell Source for Production of Immune Cells

Immunotherapy to cure anticancer has been in operation, and it involves the natural killer cells and chimeric antigen receptor T cells. Often the patient's own cells used to drive these clinical grade immune cells, stimulate them, transduce using CAR designs, amplify and then re-infuse the cells. This suggests that it is still challenging to control the number and quality of cells utilized in immunotherapy, especially in things like extensive chemotherapy or old age. Moreover, these CAR immune cells suggest in vivo anti-tumor efficacy, but it is usually limited due to their tendency to differentiate rapidly into short-lived effector cells (Bayik & Lathia, 2021). The differentiation process involves culture

of stem cells in growth media providing cytokines that trigger T or NK cells. Some of the examples of such cytokines are FLT3L, IL-15, IL-3 as well as IL-7 and SCF to enhance the growth of NK cells T cells development was induced from hESCs as well as OP9 bone marrow stromal cells by culturing both in medium containing IL-7, SFC and FLT3L (Iriguchi & Kaneko, 2019; Leone & Powell, 2020). Interestingly, CAR induction on HSCs seems to be more beneficial for cancer therapy. In bone marrow, transplanted CAR-HSCs would differentiate and give rise to a range of immune cells with fitted CAR. These cells when coordinated would have improved immunity to attack and eliminate cancer (Lan et al., 2021).

Stem Cell-Based Anti-Cancer Vaccines

Since CSCs have been establish to have a central role in the tumor progression and metastasis, targeting them would enhance the treatment regimens which are developed in the war against cancer. Of the various approaches targeting CSCs, anti-cancer vaccines are particularly rewarding due to their strong immunogenicity that may be derived from oncofetal peptides or CSC/ESC/iPSC based whole cells. Vaccines preparation commonly involves antigens and dendritic cells; such cells are employed to activate engineered T-cells for adoptive cell therapy or to induce naive T-cell responses (Gjorgieva Ackova et al., 2016).

Due to the presence of tumor heterogeneity and rapid escape mechanisms, the oncofetal peptide-based vaccination is unable to induce immune responses adequate enough for tumor control when administered singly. The vaccines derived from whole cell lysates could be far superior to these. However, the fast emergence of CSCs knowledge still poses a challenge of extracting a few CSCs from the tumor tissue thus disallowing the use of CSCs as vaccines sources (Lu et al., 2018). Even more applications of cancer treatment could be identified if vaccines were produced from many antigens derived from ESCs or iPSCs. These two are the risks for tetratomic development and autoimmunity ignition. A higher number of immune cells combined with serum cytotoxic cytokines to support the idea that allogeneic ESCs autologous iPSC-based vaccinations were effective in eradicating tumor recurrence in mice as compared to xenogeneic ones (Arjmand et al., 2024). Vaccine treatment may not be effective due to preformed tumors, containing extremely immunosuppressive microenvironment, therefore, these vaccines should be employed only as a prophylactic measure. To increase anti-tumor immunity other therapies including chemotherapy, radiation treatment, surgery, inhibitors and adjuvants must be used (Bernardes de Jesus et al., 2020; Kishi et al., 2021).

Conclusion

Although HSC transplantation has shown beneficial in instances of hematologic malignancies, such as leukemia, myeloma multiplex, and lymphomas, GVHD is still a major concern for certain patients. It is important to note that different kinds of stem cells have been employed in different ways for anticancer therapy. Moreover, the carrying and actions of MSCs and NSCs, and their exosomes have been examined in comprehensive detail to deliver the therapeutic agents towards tumors in animal models; but the only application of stem cell carriers as a treatment modality called “suicide gene therapy” is listed to trials. Despite its benefits seen in preclinical and clinical studies, there are several critical barriers to overcome of stem cell treatment. In other words, while today the stem cell technologies demonstrated quite high efficacy of tumor therapy, more research is required to make their application safer and more effective for clinical trials. Furthermore, more primary studies would be performed to elucidate how stem cells communicate with tumor progression and metastasis under specific circumstances, so that the best stem cell engineering strategy could be chosen. Surprisingly, when combined with other drugs, including immune checkpoint inhibitors, the response to tumors with micro metastases and immune-mediated tolerance to cancer cells may be superior to current treatments for establishing cancer-free outcomes and preventing recurrence due to immune suppression and heterogeneity of the solid tumor environment.

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