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CLINICAL APPLICATIONS OF STEM CELL THERAPY IN THE FIGHT AGAINST CANCER

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Abstract: Stem cell therapy is emerging as a novel approach in the fight against cancer, with over 300 clinical trials exploring various stem cell types, including embryonic, adult, fetal, amniotic fluid, and human embryonic-like stem cells. These trials aim to treat a range of diseases, notably cancer, by leveraging the regenerative capabilities of stem cells. Cancer stem cells (CSCs), a subpopulation within tumors, are integral to tumor growth and resistance to conventional treatments due to their self-renewal properties. Innovative strategies, such as suicide gene therapy using genes like Cytosine Deaminase (CD), show promise in targeting these CSCs and enhancing treatment outcomes. This review discusses the dual role of stem cells in cancer therapy, highlighting their potential to both promote and inhibit tumor development, and underscores the need for well-characterized therapeutic stem cell banks equipped with anti-tumor genes. Future research directions and the potential of stem cell-based therapies to revolutionize cancer treatment are also explored.

Keywords: Cancer stem cells, Development, Therapy

Introduction

Currently, there are more than 300 clinical trials with stem cells listed in clinical trial register. In more than 120 trials, embryonic stem cells are planned to be injected in human patients. These embryonic stem cells (44 trials), adult stem cells (175 trials), fetal stem cells (24 trials), amniotic fluid stem cells (13 trials), human embryonic-like stem cells (8 trials) are either planned or ongoing to be injected in patients suffering from diseases like diabetes, hypertension, paralyzed cord, graft failure, ophthalmic disorders, blindness, brain stroke, hair loss, coronary artery disease, chronic pain and other disorders [1]. Stem cells are being used in many clinical trials for regenerative purposes. There are promising results for stem cells in the treatment of several diseases including cancer. There is an urgent need to establish well-characterized therapeutic stem cell banks equipped with anti-tumor genes and tumor regression enzymes for the safety and

efficacy of patients receiving such cells. The cancer stem cell model relies on postulating that malignancies arise from a subpopulation of cancer cells displaying stem-like properties. Recent evidence indicates that tumors contain hierarchically organized subpopulations of cells. Some comprise the majority of differentiated progeny while a small number have stem-like properties [2]. These cancer stem cells have the distinctive abilities of self-renewal and initiating tumor growth upon transplantation into immunodeficient mice. Among regimen target, combination drugs targeting specific carcinogenic genetic/phenotypic signal transduction in tumor stem cells and non-stem progeny in parallel could minimize toxic than blanket anti-tumor drugs. Cyto-therapeutic agents that induce apoptosis include 5-fluorouracil (5-FU) and its derivatives, leucovorin (LV) plus oxaliplatin. Cancer is the leading cause of deaths worldwide. Cancer cells are either target for lysis by immune cells or generate hazardous tumors. One of the innovative approaches to treat cancer is suicide gene therapy. A suicide gene can be defined as a gene, which when transferred to an appropriate cell type would make the host cell susceptible to damage/death from otherwise innocuous prodrugs. This approach is ideal for stem cells targeting tumors. Cytosine Deaminase (CD) is one of many suicide genes used in cancer gene therapy to sensitize tumor cells to chemotherapy. CD encodes an enzyme (cdase) that converts non-toxic 5-flurocytosine (5-FC) to toxic 5-fluorouracil (5-FU) and 5-FU is a potent chemotherapeutic drug and has significant anticancer effects for regression tumor. This newly proposed CD-expressing stem biotech could offer a promising treatment for most types of solid tumors and minimize side effects on normal healthy tissues. [3,4].

Background and Significance

In the fight against cancer, stem cells are being explored for innovative therapeutic approaches. Stem cells ensure the continuous regeneration of damaged tissues and organs. Unfortunately, these properties can be hijacked by cancer cells to fuel their growth, metastasis, and recurrence. Stem cells must acquire common hallmarks of cancer to promote tumorigenesis. However, recent evidence indicates that some stem cells can actively resist tumor development and progression by reverting malignant cells to a quiescent state, thus underscoring the dual role of this versatile cell type in the context of cancer [5].

Herein, systemic data retrieved from PubMed Central, Sci-Finder, Science Direct, and Research Gate is first critically discussed, focusing on the diverse populations of stem cells endowed with anti-cancer potentials. Moreover, cancer hallmarks and mechanisms of how cancer stem cells (CSCs) become resistant to each treatment modality are also introduced [1]. Concerns regarding the safety, efficacy, and mechanisms of stem cells in a clinical setting are highlighted to devise future novel research directions. Finally, future perspectives of applying stem cells concerning the current state of knowledge of tumor biology are considered to fight against deadly malignancies.

Objective of the Work

This essay aims to investigate the clinical applications of stem cell therapy in the fight against cancer. In order to discuss this issue, it will focus on specific objectives, such as understanding the basic properties of stem cells, outlining the causes and mechanisms of cancer initiation, exploring the association between cancer and stem cells, comprehending the role of stem cells in cancer development, and discussing the potential of stem cell-based therapies to eradicate tumors. Therefore, stem cell therapy has attracted attention as a novel and promising therapeutics to combat cancer.

Additionally, stem cell therapy has the potential to regenerate healthy cells and tissues and has recently emerged as a novel mode of treatment for many diseases [6]. Based on their pluripotency, some stem cells are able to differentiate into various types of blood cells and thereby possess the potential to restore their functions. When combined with chemotherapeutics and apoptosis-inducing agents, stem cells can downregulate intrinsic pathways of malignancies and apoptosis, enhancing efficacy on tumor regression. To date, paracrine effects of stem cells have been determined as a predominant mechanism in the suppression of tumor growth and metastasis

[7]. Upon intravenous infusion, stem cells could migrate toward tumor tissues and secrete various cytokines, chemokines, and proteins to inhibit malignancy. Growing evidence suggests that stem cells possess an anti-cancer property. Hence, the application of different stem cell types as a novel class of anticancer drugs has attracted increasing attention.

Definition and Types of Stem Cells

A stem cell is defined as an undifferentiated cell of a multicellular organism that is capable of giving rise to several types of cells. Stem cells can be divided into two main categories; embryonic stem cells and somatic (adult) stem cells. Depending on the potential to differentiate, embryonic stem cells represent the highest possible developmental potential. They are pluripotent stem cells that can differentiate into any type of cell or tissue in the body. In contrast, depending on the development stage, somatic stem cells can be found in several tissues and organs in the grown organism [3]. However, they are multipotent stem cells with limited potential to develop only into certain cell or tissue types. Moreover, some adult tissues contain unipotent, tissue specific stem cells [1]. These stem cells play a crucial role in cell maintenance and tissue homeostatic control during growth, maturation and life cycle. [4,5,6]

Basic Principles and Mechanisms of Stem Cell Therapy

Stem Cell Therapy focuses on the use of stem cells as intermediates or building blocks, which have the innate potential for differentiation, proliferation, and organ rejuvenation or reconstruction. Hematopoietic stem cell (HSC) injection is the preferred route of administration for seeding stem cells in or outside the body through the veins. Stem cells target specific sites in the body and release regenerative elements and paracrine secretions, promoting the activation of dormant stem cells and reinforcing their recovery. Several clinical studies have been undertaken, and innovative techniques are also being developed for stem cell localization or capacity improvement [1].

The existence of stem cells in most of the adult organs, with the exception of very few, has been experimentally proven. The starting point to possible therapeutic applications is the development of human embryonic stem cells (hESCs); these are cells derived from the inner cell mass (ICM) of the blastocyst stage of preimplantation embryos. Accumulating evidence indicates that hECSs derived or expanded in vitro have the potential to give rise to authoritative cells of the three germ layers (endoderm, mesoderm, and ectoderm) and of primordial germ cells. The intricate mechanisms that regulate the fate of these early pluripotent cells are not yet completely understood. Meanwhile, it is now clear that pluripotent cells exist in the inner mass of blastocysts of human embryos, and with the necessary ethical assurance, these would be the ultimate source of pluripotency cells that could be adeptly used for regenerative medicine applications [7].

Cancer Biology and Current Treatment Strategies

Cancer is a complex disease that arises from the accumulation of genetic and epigenetic alterations, which lead to the transformation of normal cells into malignant cells [8]. The process of cancer development, or tumorigenesis, occurs in several stages that correspond to the progression from a normal, healthy state to a malignant one. The earliest events in tumorigenesis involve the acquisition of genetic abnormalities in a normal cell, resulting in aberrant signaling pathways that promote uncontrolled cell proliferation. Such alterations include over-activation of proto-oncogenes, loss of tumor suppressor genes, or defects in tumor suppressor genes involved in DNA repair, consequently leading to genomic instability [9].

During tumor progression, oncogenic mutations accumulate in a clonal manner, promoting distinct traits that confer a growth advantage. In the late-stages of cancer progression, the tumor exhibits uncontrolled growth and invasion. At this stage, one of the most important hallmarks of malignancy is the ability to evade the immune system or inactivate the anti-tumor immune responses. In addition, due to the continuous cross-talk between tumor cells, the stroma and the immune cells, an immunosuppressive microenvironment is established around the tumor, dominated by suppressor immune cells. In late-stage cancers, the consequent immunoediting of these tumoral immune suppressor cells promotes other facets of malignancy, such as angiogenesis.

Cancer is predominantly treated with surgery, chemotherapy, and/or radiotherapy, based on the stage of the disease. Surgery is the mainstay of treatment for localized malignancies (i.e. with no evidence of regional or distant metastasis). However, the presence of micrometastases severely compromises the efficacy of surgery. Current medical treatments are based on the use of ionizing radiation or cytotoxic drugs. Both types of treatments are designed to kill rapidly dividing cells, targeting the inherent phenotype of the majority of cancer cells. However, these types of therapies also harm normal actively dividing cell populations, such as those of the hematopoietic system, gut epithelium, and hair follicles, hence causing the main side effects associated with chemotherapy and radiation.

Understanding Cancer Development and Progression

Cancer is a complex group of diseases with multiple causes, resulting in abnormal cell growth and metastasis. Genomic studies have identified [1,3,9] driver genes associated with four major cancer types: breast, colorectal, lung, and prostate. The process of initiation involves multi-step mutations that lead to tumor development from a precursor lesion through dysplasia to carcinoma in situ. Promotion involves growth stimuli resulting from aberrant signaling pathways activated by oncogenes and inhibited by tumor suppressor genes. Tumors acquire heterogeneity through genetic and epigenetic alterations. Invasion involves the degradation of the extracellular matrix (ECM), allowing tumor cells to escape from primary foci and invade surrounding stroma. Tumors may also induce angiogenesis, increased vascular permeability, and lymphangiogenesis to support their growth and dissemination. Intravasation enables tumor cells to enter the blood circulation and exit the blood circulation by extravasation [9].

Metastasis is a multi-step process that occurs within both the primary tumor and the distant microenvironment. The process can be arbitrarily partitioned into a series of discrete steps, including local invasion, intravasation, and transport through the circulatory system, extravasation, and colonization at the distant organ. Local invasion occurs in the context of the primary tumor, whereby tumor cells escape from the primary foci and invade the surrounding microenvironment 8. The acquisition of invasive potential is often accompanied by the acquisition of an epithelial-mesenchymal transition (EMT), triggering the loss of adhesion molecules and gain of motility, protease expression, and resistance to apoptosis. The invasive process also requires the degradation of the extracellular matrix (ECM) surrounding the tumor, which is supported by the overexpression of matrix metalloproteinases (MMPs). [10, 11, 12].

Overview of Traditional Cancer Treatments

The prolonged battle with cancer has left humanity no shortfall of globally accepted treatments, the most traditional of which include surgical resection, chemotherapy, and radiotherapy [13]. These treatment modalities, alone or in synergy, have been the mainstream in cancer treatments. Surgery is performed when the tumor is localized. In most cases, the affected tissues and some surrounding tissues are removed. When surgical approaches become unmanageable, highly invasive, or impossible, chemotherapy and/or radiotherapy are employed. The vast majority of cancer cases are treated with combinations due to advantages over individual treatment paradigms. The aim is to maximally damage tumor cells while simultaneously minimizing damages to normal cells. However, these treatments have manifested several setbacks, and there is an utmost need for advanced treatment strategies for better management of cancers.

Cancer is a dynamic biological entity, with cells constantly undergoing genetic and epigenetic alterations that can lead to phenotypic variations within the tumor population [9]. These variations result in sub-clones coexisting within a tumor with genotypic and phenotypic differences. Generally, such variation is considered the root cause of cancer malignancy. Given that, even the most advanced therapy, including combinatorial strategies, can exert selection pressures on the treated tumor cells, the surviving tumor cells further adapt to new surroundings, and thus being desensitized to second-line treatment options. The majority of current cancer treatments are cytotoxic, targeting highly proliferating cells, which ultimately eliminates the bulk of the tumor population (stem cell-like cells perse), establishing a new equilibrium by favoring

slower-growing cells, and leading to treatment-resistant recurrences. Therefore, it is vital in search of better alternatives that target genotypically and phenotypically uniform populations or even single cells to build up cancer treatment courses that cannot be circumvented. Such a treatment paradigm is the administration of stem cells. [14, 15, 16]

Stem Cells and Cancer

Stem cells are undifferentiated cells found in multicellular organisms that can undergo self-renewal and generate diverse differentiated cell types. They can be categorized into two types: embryonic and adult stem cells. The former is pluripotent stem cells obtained from the inner cell mass of a blastocyst stage embryo that can develop into any cell types in the body, while the latter is multipotent stem cells found in many tissues that maintain tissue homeostasis and have regenerative capacity upon injury 8. Adult stem cells have been identified in almost all tissues and organs in the human body. They include hematopoietic stem cells (HSCs), mesenchymal stem/stromal cells (MSCs), neural stem cells (NSCs), intestinal stem cells (ISCs), skin-derived stem cells (epithelial stem cells), and liver stem cells. In addition to endogenous adult stem cells, there are also postnatal or perinatal stem cells. Postnatal stem cells are obtained from children (cord blood, cord tissue, dental pulp stem cells), while perinatal stem cells are obtained from the fetal tissues, such as placenta and amniotic fluid.

Although tumors are composed of heterogeneous cells with varied differentiation states and specialized cellular functions, evidence shows that tumors contain a subpopulation of cells with stem cell-like properties that drive tumorigenesis, tumor initiation, and metastasis, termed cancer stem cells (CSCs) or tumor-initiating cells (TICs). Clinically, CSCs are believed to be responsible for tumor recurrence after radiotherapy or chemotherapy. CSCs were first isolated from human acute myeloid leukemia samples in 1994, which expresses the CD34+CD38− surface marker pattern 1. Afterwards, CSCs were successfully isolated from various tumors, including brain tumors (CD133+), breast cancer (CD44+CD24−), colon cancer (CD133+), liver tumor (CD90+), ovarian cancer (CD44+), prostate cancer (CD44+), pancreatic cancer (CD24+), and nasopharyngeal carcinoma (CD44+). Since then, a large body of studies has focused on the role of stem cells in tumor biology. Understanding the role of adult stem cells in maintaining tissue homeostasis and regeneration of damaged tissues upon injury would benefit understanding the role of stem cells in tumor biology and therapy.

Types of Stem Cells

In their most basic characterization, stem cells are defined as cells that are able to undergo self-renewal and differentiation. These remarkable properties enable stem cells to regenerate missing tissue cells during development as well as in the postnatal stages of vertebrate organisms. Developmental biology research has led to the discovery of and distinction of different types of stem cells based on their potency and differentiation potential. Totipotent, pluripotent, and multipotent stem cells can give rise to multiple tissue types. Recently discovered cancer stem cells (CSCs) are distinct with respect to potency and potential applications to normal stem cells 9. Here, these various types of stem cells are characterized, and their significance in normal development and cancer is discussed.

Among a population of cells, stem cells are determined to be the most immature in terms of potential for differentiation. Stem cells are defined as having the ability to reproduce indefinitely (the property of self-renewal) and to give rise to more specialized cell types (the property of differentiation). More specifically, most stem cells undergo symmetric division producing either two identical stem cells (self-renewal division) or two differentiated daughter cells (differentiation division) [10]. When stem cells encounter differentiation cues, mechanisms must ensure that symmetric differentiation divisions are capped and that self-renewal divisions predominate amongst divided stem cells. If lost, malfunctioning self-renewal and differentiation divisions would disrupt tissue homeostasis and lead either to stem cell depletion or to uncontrolled proliferation of progenitor cells capable of giving rise to tumors.

Role of Stem Cells in Cancer Development

Significant advances in decomposing molecular pathways regulating certain pluripotent cells, mainly embryonic, have been achieved. Adult stem cells, which reside in a specific niche in adult tissues, also possess a similar pluripotent phenotype [11]. They exist in quiescence and become activated only under certain conditions, such as tissue injury, to restore homeostasis. Cell cycle re-entry and fate specification occur in a coordinated manner, with stem cells responding to a broad range of systemic signals simultaneously activating numerous intracellular pathways. Concluding observations were made on mesenchymal stem cells known to differentiate into osteoblasts, adyphocytes, and chondrocytes after WNT pathway activation. Such chaotic transition states impede the differentiation of normal stem cells and might drive malignant transformation.

According to the current understanding of cancer's origins, mutations either in adult tissue stem cells or in their progeny can generate a spontaneous tumor comprised of genetically abnormal cells. All solid tumors are believed to arise from just a single progenitor. However, by the time it is detected, a tumor consists of a heterogeneous mixture of genetically abnormal, phenotypically distinct cells [1]. A number of recent experimental observations are compatible with the notion that the existence of a specific cellular subtype is required for tumor growth maintenance. Such cells possess unlimited self-renewal, multipotent differentiation capacity, and ability to give rise to a more differentiated progeny.

Stem Cell Therapy

Under normal physiology, tissues of multicellular organisms are regularly maintained through the continual turnover of somatic stem cells. As they divide symmetrically, the differentiating daughter cells migrate out of the niche into the surrounding tissue, where they undergo a series of terminal differentiation steps. Based on these principles, and following the discoveries of the ability of somatic cells to acquire pluripotency, there is growing interest in the application of stem cell therapy as a novel approach for the treatment of various diseases including cancer [1]. In vitro, somatic stem cells readily form spheroidal organoid cultures in non-adherent low attachment conditions. The resulting spheroids self-assembled in a spherical form and mimicked the in vivo cellular organization. During recent years, spheroidal organoid culture systems have gained attention as novel experimental models for studying fundamental aspects of the physiology, and pathology, including tumor growth, metastasis, and drug susceptibility of stem cells in a cell-cell and cell-microenvironment context. Nonetheless, these studies were largely performed using mouse tail-tip-derived skin epithelial stem cells either in a non-contact co-culture with fibroblasts or without any stromal component [5]. There is growing interest in the use of customized therapeutic stem cells, genetically engineered with tumor regression genes, to create stem cell banks for the treatment of a variety of diseases including cancer. Banks of such stem cells would allow for consistent, reliable, and effective treatment protocols preventing variation in treatment effects. Hence, the formation of these specialized therapeutic stem cell banks should be encouraged[29,30].

Principles and Mechanisms of Stem Cell Therapy

The treatment of cancer, one of the most devasting and above the common human health problems worldwide since long, requires the development of better options and techniques which are more efficient and safe. Presently, the options are very limited with chemotherapy, radiotherapy and simultaneous surgical removal. All of these approaches have their own limitations [1,28]. Recently, the attention of the scientists and researchers has been redirected, when the science has freshened the hope of defeating or at least containing cancer with the advancements and discoveries in stem cell biology.

A variety of endogenous dimorphic stem cells are present in every organ of the body in a state of rest while in adult life some remain in the germinal niches. These stem cells, especially hematopoietic stem cells, are capable of broad differentiation into several cells of chronic nature and thus can act as a long-lasting target as well as weapon against a disease like cancer. Moreover,

neural crest stem cells are also considered good candidates for targeting the brain tumors as they specifically colonize the brain without triggering an invasive response[26,27].

The basic mechanism is to engineer these stem cells with tumor regression enzymes, cytosine deaminase (CD), which regulates the conversion of inert compound, 5-fluorocytosine (5-FC), to cytotoxic compound, 5-fluorouracil (5-FU) inside the tumor cells. In addition to enzyme-engineering, anti-cancer genes may also be introduced in the therapeutic stem cells. Well-characterized therapeutic stem cell banks equipped with tumor regression enzymes, anti-tumor genes and transduction viruses are the potential tools for prompt clinical application and research endeavors on stem cells [7].

Types of Stem Cell Therapies

Two major types of stem cell therapies are utilized in the clinical fight against cancer. The first type involves hematopoietic stem cell transplantation (HSCT) which is widely employed to treat leukemia and inherited blood disorders. HSCT utilizes stem cells from either bone marrow, peripheral blood, or umbilical blood. These stem cells can be autogenic (from the patient) or allogenic (from a compatible donor). In preparation for HSCT, the patient must undergo total body irradiation and chemotherapy that destroys cancerous blood cells but also impedes hematopoiesis. Subsequently, stem cells are transplanted to provide a new population of healthy cells and re-establish hematopoiesis 1. Although HSCT can promote anti-tumor immune responses (graft versus leukemia effect), its effectiveness can be adversely affected by chronic graft versus host disease (GvHD) [9].

The second type involves the use of mesenchymal stem cells which are multilineage adult stem cells that are naturally present in the bone marrow and other tissues. Basic research has shown that MSCs can recognize and migrate towards tumor areas. As a result, they have been engineered to overexpress anti-tumor agents, including cytokines that can boost the immune system (e.g. GM-CSF, IL-12), enzymes that can convert prodrugs to cytotoxic compounds (e.g. cytosine deaminase) or induce apoptosis (e.g. herpes simplex virus thymidine kinase), and small interfering RNA that can silence anti-apoptotic proteins and resistance proteins. Transplantation of these genetically modified MSCs that express anti-tumor agents can effectively delay tumor growth in mice;. However, several problems must be addressed, including tumor-induced immunomodulatory effects on MSCs. In some cases, these immunomodulatory effects suppressed the activity of MSCs and dampened immune response while promoting angiogenesis and proliferation of tumor cells. [12,13,14]

Current Clinical Trials

Stem cell therapy emerged sixty years ago and was almost exclusive to the treatment of hematopoietic disorders. As a natural consequence of both advancement in science and technology and reliable clinical experience boundary, a growing number of diseases are now being considered for stem cell treatment, including cancers, neurodegenerative diseases (Parkinson’s and Alzheimer’s diseases), cardiovascular diseases, rehabilitation after stroke or trauma, and congenital diseases [6]. There have been several pre-clinical and early-stage clinical studies to test the efficacy and safety of stem cell therapy for cancers. These studies have shown promising preliminary results.

The studies report that systemic or local injection of stem cells leads to a significantly reduced tumor size, and increased survival rate. A possible mechanism behind the tumor regression may be due to the stem cell-mediated targeting and destruction of malignant cells. However, there are still many variables which should be addressed before the masses can benefit from the treatment of cancer by stem cells [1]. Full understanding of the expression profile of stem cells in vivo as they migrate towards the tumor site is essential in order to identify the characteristics of stem cell types and enhance their efficiency in suppressing the tumor. Stem cells can be divided into embryonic stem cells and adult stem cells. Being pluripotent, embryonic stem cells (ESCs) have the capability to divide indefinitely and are able to give rise to any cell type of the body. They hold great promises for regenerative medicine and development of novel therapies

for currently incurable diseases such as diabetes and Parkinson disease[25]. However, their clinical application is severely hampered by ethical concerns, technical difficulties, immunogenicity and tumorigenicity. The adult stem cells, on the other hand, are multipotent, having the restricted capacity to self-renew and generate a limited number of different cell types. But they still have the risk of tumorigenicity. In general, stem cells have low immunogenic reactivity, making them potential candidates for another class of therapeutic agents different from drugs. [15,16]

Promising Results and Challenges

Stem cell therapy has emerged as a groundbreaking and innovative form of medical treatment for a diverse range of diseases, including cardiac conditions, neurodegenerative disorders, and more recently, cancer. The primary objective of utilizing stem cell therapy for cancer treatment is to eliminate cancerous tumor cells by either impeding their uncontrolled proliferation or altering them in a manner that renders them incapable of forming metastatic cancer growths[24]. Presently, there are numerous ongoing international clinical trials which aim to explore the efficacy of different types of stem cells that have been modified in various ways, employing diverse approaches to target different forms of cancer. The overarching aim of these trials is to glean valuable insights from the promising results and to address the challenges encountered along the way. Ultimately, the objective is to uncover effective methodologies that can be employed to combat these aggressive diseases through the application of stem cell therapy. By shedding light on the outcomes of these ongoing trials, it is hoped that the medical community can move closer to successfully harnessing the potential of stem cell therapy in the battle against cancer. [1, 17, 18, 16]

Assessment of current clinical trials involving stem cell therapy for cancer reveals some promising preliminary results but also a variety of challenges which must be tackled before stem cell therapy for the treatment of cancer becomes widely available as an innocuous effective therapeutic option for cancer patients worldwide [6].

Future Directions and Implications

The Voice of the Customers (VOC) can be defined as the entire range of customer needs, wants, and preferences about a product, service, or organization. For example, based on customers' feedback, it is possible to identify specific products related to each requirement, as well as its importance and satisfaction level. The VOC determines the product features, level of performance, and design specifications that must be taken into account when developing a new product or improving an existing one. Solution ideas may arise naturally from each requirement, thereby becoming a set of possible design concepts for each of them. Ultimately, VOC helps to assess the fitness-for-use of each design concept, to prioritize the design concepts that will be included into a new product, and to redesign the product if the assessment shows that it does not meet the customer requirements.

It is expected that there will be a continuation of heightened interest and investment in stem cell therapies and research in cancer for the foreseeable future. The possibility of advancements from stem cell therapy in this field can and will most likely take many forms and pathways leading to the cure of cancer and making a positive impact to the cancer landscape. However, one of the most defenses taken in the future would have to be the thought and knowledge that through biological advancements, tumor resection, chemotherapy, and even targeted therapy may one day be extinguished as the norm in the scientific fight against cancer. Even though there is still much research and work to be done, stem cells may one day serve as anything from alternative steps to treat lesions and masses to the means to fully replace existing techniques while leaving positive impact on the patient's health and wellness state[23].

Potential Advancements in Stem Cell Therapy

As the field of stem cell therapy continues to evolve, several cutting-edge technologies and approaches are emerging that promise to shape the future of this powerful tool in the fight against cancer. Gene editing techniques, such as CRISPR/Cas9, have the potential to render stem

cells therapeutic by enhancing their immunogenicity or by constructing cellular “soldiers” that deliver high doses of anti-tumoral agents directly to the tumors [7]. Programs of induced pluripotent stem cell (iPSCs) generation and storage in bio-archives offer the possibility of developing biobanks from different individuals, thus making it possible to study the influence of genetic variability or obtain standardized stem cell products for widespread clinical application. Furthermore, 3D biomimetic in vitro models of tumors, developed with the aid of bioengineering techniques, are proving to be an asset for basic research and drug screening and are expected to ease the translatability from bench to the clinical application of newly discovered drugs and therapeutic technologies [6].

The recent successful experiences gained from the reprogramming of human skin fibroblasts into pluripotent stem cells have opened new avenues for innovative strategies of induced differentiation of hPSCs. Using these new strategies together with global epigenetic reprogramming approaches would make it possible to generate somatic cells from different individuals, thus providing an unlimited source of patient-specific cells for a wide variety of cell therapy and research applications. This suite of technologies is contributing to the advancement of the two major stem cell-based strategies for treating cancer: using stem cells as anti-tumoral agents or as the source of cells for regenerative medicine. The successful implementation of these approaches will depend on the broad accessibility of novel methods and material development for the generation of either “therapeutic” stem cells or “safety-net” technologies that allow a better regulation of their therapeutic cell product[22].

Conclusion

Clinical applications of stem cell therapy offer fresh perspectives in the resolution of worldwide cancer. As germinal elements of heterogeneous neoplasm, cancer stem cells (CSCs) potentially exert the drug resistance, enactment of metastasis, recurrence, and so forth. When taken into clinical practice, stem cells from various sources, along with various modifications, are employed with adjunct strategies to enhance the efficacy for the regression of malignancy. Generalized pathway of clinical approval usually commences from laboratory investigation into animal studies, then into prospective clinical trials under the guidance of local regulatory bodies, such as FDA in the USA. It takes great efforts participation of scientists, practitioners, and entrepreneurs, and lasting time for years to decades. However, with regards to novel CSC targeting therapy, it is urgent to meet with rapid trial methods to facilitate advancement and investigations.

The approaching resolution of stem cell therapy is to exhibit multiple biological functions for cancer treatment. Underlying the plasticity, paracrine tropism and angiogenic capacity of particular type of stem cells provide the impetus for smart design and control of smart biomaterials. Through ligand-receptor interaction and immuno-masking, recent prostate CSCs targeting MSC-EpCAM mAb-encapsulated nanoparticles could provide an innovative approach to eliminate CSC population. Though sophisticated, the systemic display of biological functions via natural selection is far less organic than endogenous target. Thus, future investigations shouldn’t restrict the lineage of paracrine tropism. Further studies should embrace with the usage of stem cells from other tissues like spleen, skin, and liver, and the paired examination of comparative paracrine effects on neoplasia as well, which may confer novel aspects into cancer metastasis and drug development.

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