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Need for Specialized Therapeutic Stem Cells Banks Equipped with Tumor Regression Enzymes and Anti-Tumor Genes

Mujib Ullah*
Interventional Regenerative Medicine and Imaging Lab, Department of Radiology, School of Medicine, Stanford University, California, USA.

*Corresponding Author:

Mujib Ullah, Dr. Medic, PhD
Department of Radiology, Stanford University
3155 Porter Drive, Palo Alto, CA, 94304, USA
E-mail: ullah@stanford.edu

Abstract

Stem cells are currently being used in many clinical trials for regenerative purposes. These are promising results for stem cells in the treatment of several diseases, including cancer. Nevertheless, there are still many variables which should be addressed before the application of stem cells for cancer treatment. One approach should be to establish well-characterized therapeutic stem cell banks to minimize the variation in results from different clinical trials and facilitate their effective use in basic and translational research.

Keywords:
Stem cells banks, Cancer, Cytosine deaminase, Tumor, Gene therapy

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1. Introduction

Cancer is the leading cause of deaths worldwide [1, 2]. One of the most innovative approaches to treat cancer is suicide gene therapy [3, 4]. Cytosine Deaminase (CD) is one of many suicide genes used in cancer gene therapy to sensitize tumor cells to chemotherapy [3, 5]. CD encodes an enzyme that can convert non-toxic 5-flurocytosine to toxic 5-fluorouracil (5-FU) [3, 6]. 5-FU is a potent chemotherapeutic drug and has significant anticancer effects for regression of tumors [3, 5]. One limitation of previous reports was to engineer CD gene into viruses or mesenchymal stem cells (MSCs) [5, 7, 8]. Viruses are protumor in some cases and are relatively poor in targeting tumor cells [5, 7, 9]. The use of viruses can also pose a risk to patients in a variety of ways by triggering immune and inflammatory reactions [5, 7, 9]. Furthermore, viruses cannot distinguish between normal and cancer cells and have the capability to self-recover and cause diseases once inside the body [5, 7, 9]. On the other hand, MSCs offer great therapeutic promise to treat cancer patients [10-12]. However, the clinical trials of MSCs are hindered by many factors like considerable donor variations, epigenetic reprogramming, senescence in culture, protumor potential of MSCs under certain conditions, limited expandability, and difficulty for transgene expression [11-15]. Additionally, the epitopes to define MSCs are still not very specific, and differentiation assays are difficult to standardize [12, 13, 16-18]. One solution may be to establish huge repositories of standardized iPSCs-derived MSCs banks for worldwide distribution that can be shared with scientists and clinicians across the globe [19]. The insertion of therapeutic genes into these iPSCs can make them more tumor precision-based banks [3, 5]. The use of iPSCs-derived MSCs has an advantage over bone marrow–derived MSCs, as they grow in less time and propagate more, undergo more population doublings, experience less growth-arrest in culture, and have better healing abilities [3, 12, 13]. Importantly, they did not form teratomas, and they are less impacted to genetic drift and mutations [12, 13].

The iPSCs-MSCs have strong tropism toward cancer cells and can serve as cellular vehicles to deliver CD within or near the tumor sites [6, 13]. The beauty of this approach is that iPSCs-MSCs with CD itself can undergo cell death caused by suicide effects of 5-FU, ensuring the long-term safety of this method [3, 5]. After suicide action of these cells, there is no leftover gene [3, 5]. Thus, it eliminates the concerns like insertional mutagenesis, gene activation in long-term effects commonly associated with such therapies [5, 13].

In case of challenging brain tumors, iPSCs-MSCs could be designed to treat the remaining tumor masses after surgery to minimize tumor reoccurrence chances in patients [5, 20]. After administration of this therapy, once the prodrug starts destruction of the cancerous cells, this process may also prompt the immune system to attack the tumor cells [5, 20]. This strategy can be effective to treat recurrent cancer patients who received a standard treatment (surgery, radiotherapy, and chemotherapy).

These therapeutic cells can be freshly prepared from standardized master banks and can be given to patients who qualify for such kind of therapy [21]. However, the master cell

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bank must be produced in a good manufacturing practice-compliant facility and should be filed to the Food and Drug Administration to assess toxicity and safety trials [21]. A safe and efficient gene carrier is a prerequisite for successful anticancer therapy, and we believe that iPSCs-MSCs can be a suitable cargo for CD enzyme [3, 5]. Whether or not iPSCs-MSCs with CD gene therapy make it to market is currently unclear.

2. Source of stem cells for therapeutic banks

There are several sources of stem cells, but bone marrow and adipose tissue is the best-known source for several types of cells [17, 22, 23]. Different types of stem cells are totipotent stem cells, pluripotent stem cells, adult stem cells, umbilical cord-derived stem cells, embryonic stem cells, and reprogrammed stem cells [15, 17, 23]. Recent data indicates that adipose-derived stem cells (ASCs) and bone marrow-derived stem cells (BMSCs) share many biological features; however, there are some variations in their surface epitopes, immunophenotype, differentiation potential, cytokine secretion profile, proteomic profile, and their ability to secrete growth factors [24, 25]. BMSCs and ASCs populations differ in heterogeneity, potency, doubling time, and proliferation, according to conflicting results in clinical trials [24, 25]. Most importantly, these differences support the use of induced pluripotent stem cells because they form a more uniform population and, according to clinical results, seem to be more effective [25, 26]. Many studies have shown the biology, regeneration ability, and clinical applications of iPSCs in detail [27-30]. Banked iPSCs are not only used for research but are also commonly used for clinical applications such as transplantations and the field of regenerative medicine [30]. The iPSCs that have been studied for regenerative medicine have been extensively investigated for their therapeutic potential [30]. One special feature of these cells is that they can easily produce millions and even billions of cells to prepare large banks [27, 30].

Therefore, this necessitates the establishment of a major research project to globally bank the iPSCs and to characterize them more fully with the latest techniques and instruments [31]. One approach to this can be to insert therapeutic genes for cancer prevention or diagnosis or otherwise to “pre-activate” them so that they become more powerful in healing tissues and killing cancer cells [31]. One method to derive these immortal iPSCs cells is to obtain them from essentially any tissue in adult donors [31]. One advantage of deriving iPSCs this way is that they can be used to generate an essentially unlimited supply of thoroughly standardized cells while excluding the tendency of normal iPSCs to form tumors which then presents a danger in using iPSCs in patients [26, 32]. Another advantage is that the exosomes that iPSCs produce appear to have even greater therapeutic effects than the iPSCs themselves [8, 33]. Because of these two advantages, iPSCs banks would have two strategies to treat diseases: one based on the administration of iPSCs to patients and the other based on the administration of the proteins or exosomes that iPSCs produce [26, 32].

Therefore, one can confidently state that both iPSCs themselves and their derivatives such as their exosomes are potent instruments and a great choice for banks and for later

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use in biomedicine, cell replacement therapy, and cancer prevention, furthering the need for the maximum standardization and safety [25, 34].

3. Selection of anti-tumor genes for banks

Among various treatment strategies, suicide gene therapy attracts special attention because it allows for selective conversion of non-toxic compounds into cytotoxic drugs that selectively kill the cancer cells [5, 8]. There are many suicide genes such as cytosine deaminase, the herpes simplex virus, cytochrome P450, thymidine kinase, Purine Nucleoside Phosphorylase, carboxypeptidase G2, nitro-reductase and many more [5, 34]. The cytosine deaminase enzyme, specifically, effectively kills cancer cells by converting 5-FC into toxic 5-FU, which is shown to easily diffuse into cancer cells to enhance apoptosis, and accelerate protein starvation of tumor cells, forcing them into cellular death [35, 36]. Additionally, the drug 5-FC does not need a gap junction to penetrate into tumor cells and diffuse through the blood brain barrier; this makes drug 5-FC a good choice for treating hard-to-reach tumors such as glioblastoma [37, 38]. With the introduction of high concentrations of cytotoxic molecules to the tumor environment, our current therapeutic index may be increased significantly while minimizing impact on normal tissues.
Despite significant successes already made in the field of suicide gene therapy, we should now optimize factors like transgene selection, delivery methods, enzyme engineering, transgene expression, and drug conversion rates.

4. Conclusions

Suicide gene therapy forces cancer cells to self-destruct while standard chemotherapy drugs damage both healthy and cancerous cells [5, 35]. The therapeutic consequences of suicide gene therapy can be spread beyond the transfected tumor cells [5, 36]. As a result, distant tumor lesions can be regressed [5, 20]. Suicide gene therapy could be used as an additional cornerstone step in cancer treatment along with the conventional integrated multimodality approach of chemotherapy, radiotherapy and surgery [5]. This will help in the regression of tumors and possibly prevent multidrug resistance commonly observed in cancer patients [6, 10, 11]. IPSCs genetically engineered to express CD enzymes may be a valuable therapeutic option for treating cancer, but some hurdles must be overcome before they become a clinically efficient treatment of cancers. Possible solutions include vector design to enhance targeting and controlled delivery, combination of different suicide genes, more efficient activation of a given prodrug, and the creation of better substrates for the enzymes in order to maximize drug release and to allow the active drug to accumulate more readily in tumor cells.

Banks of iPSCs are very important to preserve their characteristic stemness and potency, to prevent contamination and deterioration, and to facilitate their effective use in basic and clinical applications [3, 21]. A number of stem cell banks have already been established in many countries, and their prevalence is expected to expand [3, 21]. Concurrently, there is still a substantial need for specialized therapeutic stem cells banks in order to determine the effectiveness of iPSCs in clinical applications.

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Authors' information

Interventional Regenerative Medicine and Imaging Laboratory, Stanford University School of Medicine, Department of Radiology, Palo Alto, California 94304, USA

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