

Stem cell technology and engineering for cancer treatment

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Abstract—Stem cells are not only widely used for regenerative medicine, but are also considered as a useful tool for cancer treatment. For a long time, stem cells have been utilized to renew the immune system for radiation or chemotherapy treated patients. Recently, stem cells are being engineered to carry therapeutic reagents to target tumor sites. Cancer vaccines based on the knowledge of cancer stem cells have been studied and applied for cancer treatment. Induced pluripotent stem cells have been used to create active T cells to support cancer immunotherapy. Those are due to the unique characteristics of stem cells, such as immunological tolerance, migration, and tissue reparation. This review discusses stem cell applications in transplantation, stem cell-based carriers, induced-pluripotent stem cells, cancer stem cells, and potential of stem cells engineering to revolutionize cancer treatment.

Keywords— Stem Cells, Cancer, Stem Cell therapy, Stem cell treatment, Cancer stem cells.

INTRODUCTION

Our bodies contain a pool of stem cells that have the ability to differentiate into any other cell type in the body. Organs and tissues are built up by specialized cells from the pool of stem cells that form shortly after fertilization. Stem cells continue to play a role in repairing damaged tissue and replacing cells that are lost every day. Stem cells are widely defined by two main characteristics: the ability to self-renew (divide in a way that reproduces more identical stem cells) and to differentiate (to turn stem cells into specialized cells that form different organs and tissues).

There are many different kinds of stem cells that exist for different periods of an animal lifetime. For example, embryonic stem cells exist only at the earliest stage of embryo and adult stem cells appear during fetal development and are retained throughout life.

Embryonic stem cells were first identified in mice (Martin, 1981). Embryonic stem cells are pluripotent, meaning they are able to produce all cell types in the

body. These cells exist only in earliest stages of embryonic development known as the blastocyst stage. A blastocyst contains an inner cell mass including a clump of around 150 cells that eventually will generate the entire body of the adult animal. When these cells are isolated from the blastocyst and grown in a lab dishes, they can continue dividing indefinitely.

Recently, scientists have discovered how to reprogram normal cells to behave like embryonic stem cells. This is done by re-activating critical genes that define embryonic stem cells to make adult stem cells to revert to an embryonic-like state of pluripotency. These cells are called induced pluripotent stem cells (iPSCs).

The first iPSCs were created from normal cells in the mouse (Takahashi & Yamanaka, 2006). Later in 2007, iPSCs from human skin cells were generated by the same group and created in a number of other laboratories soon afterwards (Park, Lerou, Zhao, Huo, & Daley, 2008; Takahashi et al., 2007; J. Yu et al., 2007;

Junying Yu et al., 2007). As the name implies, pluripotent cells are able to generate all other specialized cell types. This way of making iPSCs from adult cells circumvents the need to destroy an embryo from living donor.

Adult stem cells were firstly isolated from bone marrow in mice (Spangrude, Heimfeld, & Weissman, 1988) and later in humans. Some adult stem cell lines are multipotent, in the other words, they have the ability to turn into a defined set of mature cell lines. Some adult stem cell lines are unipotent meaning that they can differentiate into only the cell type of tissue in which they reside. Adult stem cells are found in the tissue of adults, children, and fetuses. However, it is unclear if stem cells are present in all organs. Adult stem cells are rare and difficult to isolate from surrounding tissue.

Adult stem cells are considered as a resource to maintain the turnover rate of cells in the mature tissue. Normally, the body's cells grow and divide to form new cells, according to body's demands. When cells become old or damaged, they die as programmed, and new cells will take place. However, when these cells divide out of control and invade into surrounding tissue, they can cause disease, called cancer. Cancer cells do not die as they are supposed to, but they keep proliferating without the body's demand. These cells may form masses of quickly dividing cells called tumors. Many cancers form solid tumors. However, blood cancer does not form solid tumors.

Cancer is a leading cause of death worldwide, with approximately 14 million new cases and 8.2 million deaths in 2012, according to World Cancer Report 2014. Until now, there are several methods to treat cancer including surgical extraction, chemotherapy, radiation, targeted drug therapy, immunotherapy, and stem cells. Stem cells have contributed significant roles for those approaches of cancer treatment and research. Basing on unique characteristics of stem cells such as self-renew, differentiation, and damage repair, stem cells have been exploited as useful tools in supporting conventional approaches as well as in developing new methods for cancer treatment.

STEM CELL TRANSPLANTATION TO RECOVER IMMUNE SYSTEM

Stem cell transplantation (SCT) is the procedure that can recover the marrow function for patients who

have severe marrow injuries or damaged immune. Stem cell for transplantation can come from bone marrow, peripheral blood, or umbilical cord blood. There are many terms for stem cell transplantation, including bone marrow transplantation, cord blood transplantation, or hematopoietic cell transplantation. These different names are used for the same procedure. There are two common types of transplantation including autologous and allogeneic stem cell transplantation.

With autologous stem cell transplantation, patients use their stem cells. This type of transplantation is used for cancer patients who exposure with a high dose of chemotherapy or radiation therapy. Such high doses of treatment are used to eliminate cancer cells, but can severely damage bone marrow and immune system. Therefore, in order to preserve stem cells, those are collected from bone marrow or blood before treatment, then frozen. Later on, thawed stem cells are re-infused into a patient in order to restore function of the immune system (Illerhaus et al., 2006; Kessinger et al., 1991) (Fig. 1). Because stem cells come from patient's own, the immune system recovered by stem cell does not attack patient's tissue. However, those could be contaminated with circulating cancer cells and may increase the risk of relapse of disease. Furthermore, the recovered immune system could be stronger, but does not have the ability to eliminate the remaining cancer cells since those cancer cells may tolerate to patient's immune system (Igney and Krammer, 2002; O'Connell et al., 1999).

Allogeneic stem cell transplantation is typed of treatment that using stem cell from donors that are could be related or unrelated. The compatibility of tissue type, called human leukocyte antigen (HLA), between recipient and donor, is primary criteria in this type of transplantation. Since recipients receive stem cells from another person, it is possible that: immune system of patient reject donated stem cell (host-versus-graft effect), or the donor cells cause immune reaction against tissue of the recipient (graft-versus-host disease [GvHD]). However, before the allogeneic transplant, patients are treated with high doses of chemotherapy or radiation therapy. This treatment eliminates cancer cells and also suppresses the patient's immune system. Therefore, patient's immune cells are less able to attack donated stem cell. One of the most important benefits of allogeneic transplant is to generate graft-versus-tumor (GvT) effect. GvT effect is donor immune system recognizing the remaining

cancer cells that survived after high doses of chemotherapy, and eliminating them. This effect may help to reduce the risk of disease occurrence. However, GvT effect is often accompanied by GvHD, which is substantially influence mortality after transplantation. In order to reduce GvHD, patients were treated by drug to reduce the ability of donated immune cells to react with patient’s tissue. When the new immune system developed by donated stem cells tolerates to host’s tissue, the patient may reduce or stop using the drug to suppress immune cells. Various factors such as donor selection, stem cell source, immunosuppressive regimen are implemented to balance GvT and GVHD.

radiation therapy with SCT is also used for patients with solid tumors such as metastatic renal cell cancer (Burk, 2001), advanced ovarian cancer (Frickhofen et al., 2006), breast cancer (Garcia-Rayó et al., 2001), testicular cancer (Voss, Feldman, & Motzer, 2012) brain tumor (Dunkel & Finlay, 2002), Wilm’s tumor (Kosmas et al., 2010). However, recently studies observed survival SCT patients for 20 years has shown that SCT recipients have a substantial risk of developing solid secondary cancers five years after SCT (Inamoto et al., 2015). The secondary cancers include the skin, thyroid, oral cavity, esophagus, liver, brain, bone, and connective tissue. Young age at SCT, chronic GVHD, and prolonged immunosuppressive treatment are supposed to be the risk factors for many types of

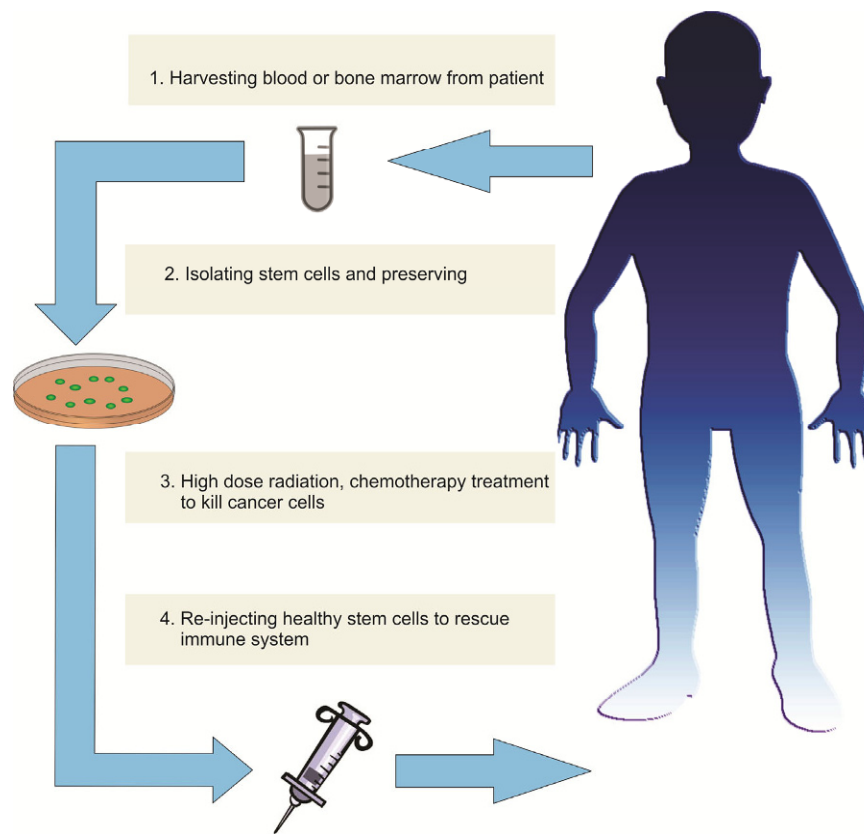


Figure 1. Autologous stem cells transplantation in cancer treatment. Stem cells are isolated from patient’s bone marrow or peripheral blood, then preserved. After patients are treated with high-doses of chemotherapy or radiation therapy to eliminate cancer cells, the immune system of patient is weakened. Stem cells are re-injected into patient to recover immune system.

Stem cell transplantation supporting high-doses chemotherapy has shown effective in treating a patient with blood cancers. High doses chemotherapy and

secondary. Another factor could involve in developing a secondary tumor. For instance, a study on survival SCT blood cancer patients has shown post-high dose sequential radiotherapy associated with risk of sec-

ondary malignancy (Tarella et al., 2011). While looking toward the improvements to prevent tumor development in survival SCT patients, SCT is still the first line for supporting high doses chemotherapy and radiation therapy in cancer treatment.

PRODUCTION OF CANCER-SPECIFIC T CELLS FROM INDUCED PLURIPOTENT STEM CELLS

T lymphocytes play an important role in the immune system and are at the core of adaptive immunity to response to specific invaders. In cancer, T-cells search out and destroy the targeted cancer cells. However, the immune system of cancer patients has shown to be modulated so that T cells do not effectively recognize and eliminate cancer cells (Baitsch et al., 2011; Beurskens et al., 2012; Fourcade et al., 2012; Oleinika et al., 2013; Prado-Garcia et al., 2012; Riches et al., 2013; Severson et al., 2015). Therefore, studies have been done to offer solutions to produce killer T cells for cancer treatment. Recently, discover of induced pluripotent stem cells (iPSCs) by reprogramming normal

cells have triggered new methods to produce cancer cell-specific killer T cells.

There are multiple ways to generate cancer cells-specific T cells through reprogramming techniques. One of those methods is generating iPSCs from mature CD8+ T cells (Fig. 2A). Mature killer T lymphocytes are reprogrammed into iPSCs by exposing them to Yamanaka reprogramming factors (c-Myc, SOX-2, OCT-4, and KLF-4). These factors are a group of genes that help specialized cells convert into a pluripotent state. The iPSCs are grown in the lab until they reach a large number; then they are induced to differentiate into killer T lymphocytes again. These differentiated killer T cells maintain the same genetic phenotype as the original killer T cells and are fully functional (Vizcardo et al., 2013).

Another way to produce specific T cells is generating iPSCs from naïve T cells instead of committed T cells. The first step is to harvest naïve T cells and then expose them to the reprogramming factors. Reprogrammed killer T cells are grown and transduced with recombination receptors for tumor-specific antigens,

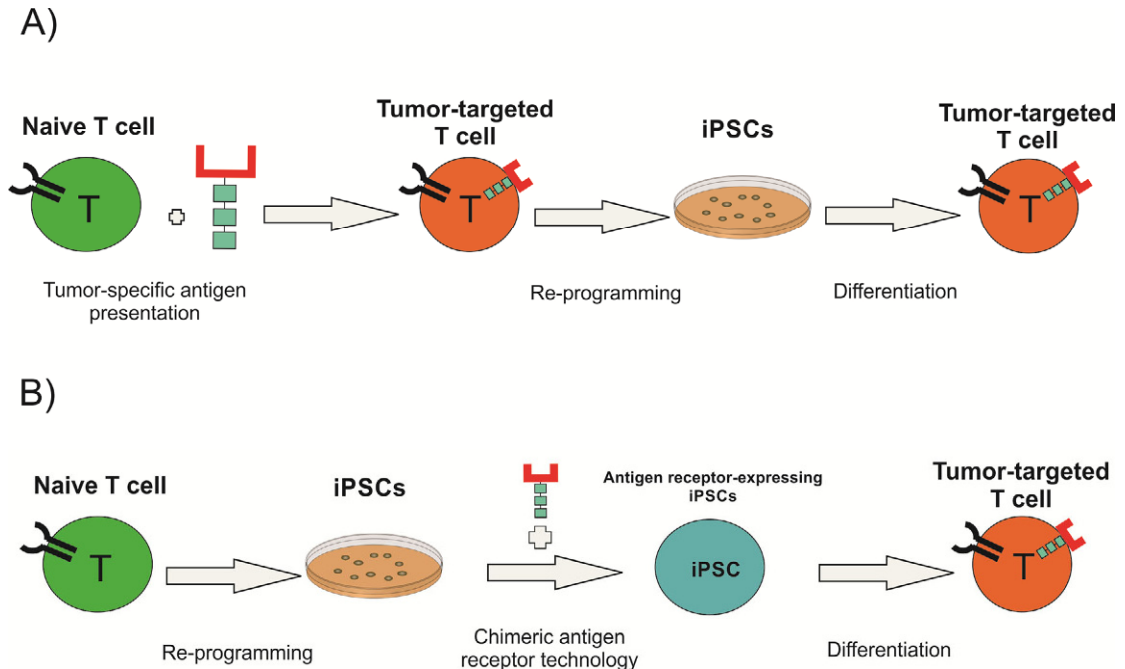


Figure 2. Generation of tumor-targeted T cell by engineering chimeric antigen receptor and iPSCs.A) Priming naïve T cells with tumor antigens, then re-programming primed-T cells into iPSCs to exploit self-renewing capability in order to get a sufficient number of cells. Finally, iPSCs are differentiated into tumor-targeting T cells. B) Naïve T cells are reprogrammed into iPSCs in the first step. These iPSCs are then engineered to express antigen receptors. Then iPSCs are expanded to the expected number and induced to differentiate into a tumor antigen-targeting T cells.

called chimeric antigen receptor (CAR). Finally, these cells are induced to differentiate into T-lymphocytes with an affinity for the chosen tumor antigen present on cancer cells (**Fig. 2B**). This technology was successfully used to create human T cells specific to CD19, a marker expressed by malignant B cells (Themeli et al., 2013). These iPSC-derived T cells have been shown to be the same phenotype as peripheral blood T cells and to possess the ability to inhibit tumor growth. Regeneration of T cells from iPSCs is potential to create a mass of therapeutic T cells for cancer treatment in the future.

STEM CELLS AS VECTORS CARRYING THERAPEUTIC REAGENTS TO TUMORS

In gene therapy for cancer treatment, stem cells are used as vehicles to carry drugs or therapeutic vector viruses to tumors. Stem cells possess two crucial advantages that determine their potential application for gene therapy: tumor tropism and immune-privilege.

Stem cells have intrinsic characteristics to migrate toward the injury sites to support repairing. Cancer is a form of lesion inside the body. Thus, mesenchymal stem cells are postulated to have the ability to migrate towards tumors. In fact, tumors secrete cytokines such as TGF- β , IL-8, EGF, HGF, FGF, and PDGF. These secreted cytokines stimulate MSCs to upregulate chemokine production and expression of chemokine receptors (Escobar et al., 2014), and then making MSCs more able to migrate to the tumor site.

Many studies have used MSCs and neural stem cells

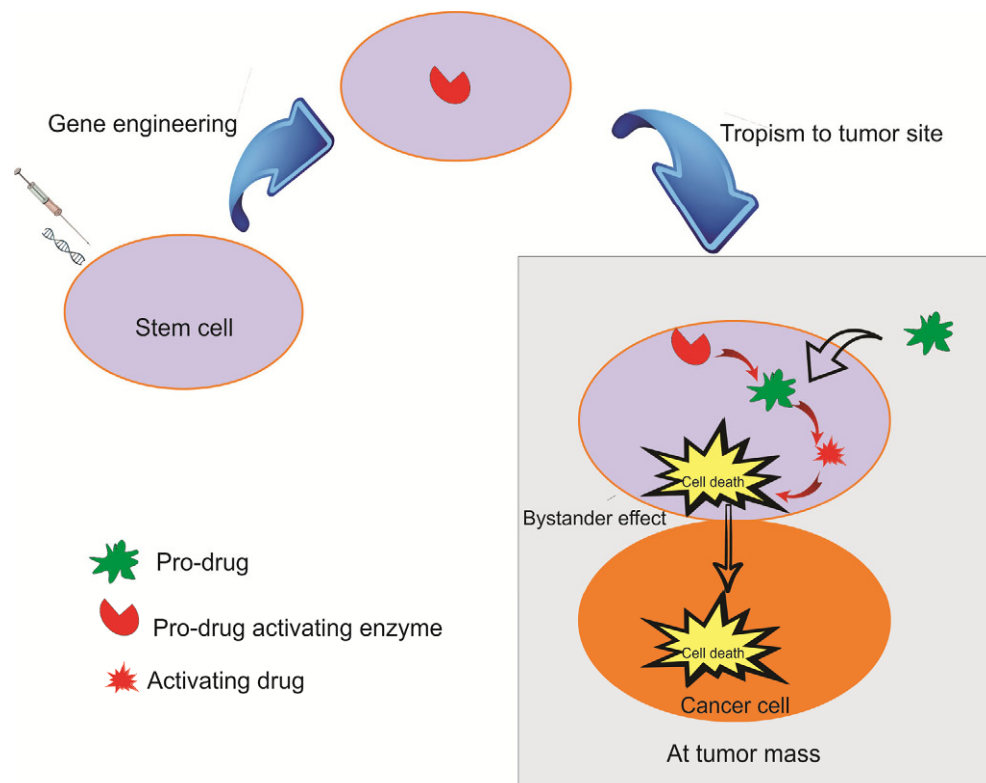


Figure 3. Stem cells carrying therapeutic reagents to tumor site. Stem cells, usually mesenchymal stem cells (MSCs), are engineered to express suicide enzymes. MSCs, with the ability to repair injury, will migrate to tumors. When penetrating into tumor site, enzyme activates prodrug into drug to kill cancer cells.

(NSCs) to carry suicide enzymes to the tumor site. This approach is expected to avoid systemic toxic effects and leave normal cells intact. Prodrug-activating systems that are commonly used are cytosine deaminase/5-fluorocytosine (Mullen et al., 1992; Wang et al., 2012), herpes simplex virus thymidine kinase/ganciclovir (Kokoris and Black, 2002). Once engineered stem cells reach the tumor, the suicide enzymes activate 5-fluorocytosine or ganciclovir to a drug that attacks crucial metabolic pathways in the cells, leading to cell death (**Fig. 3**). Active drugs are able to attack neighboring cancer cells via the gap junction, intracellular communication, and connexins; this process is known as bystander effect (Kandouz and Batist, 2010). MSCs- based gene therapy has been used to treat several diseases in animal models including glioblastoma (Altaner et al., 2014; Altanerova et al., 2012; Fei et al., 2012; Lee et al., 2009), prostate cancer (Cavarretta et al., 2010), melanoma (Kucerova et al., 2008), gastrointestinal cancer (You et al., 2009), and other malignancies. Along with MSCs, neural stem cells (NSCs) carrying suicide enzyme have shown to reduce tumor volume and to increase survival in mouse model of malignant disease including medulloblastoma (Kim et al., 2006), melanoma brain metastases (Aboody et al., 2006), glioblastoma (Barresi et al., 2003; Ito et al., 2010), breast cancer brain metastases (Joo et al., 2009), prostate cancer (Lee et al., 2013), and breast cancer (Yi et al., 2014).

Stem cells are also utilized to delivery immunostimulatory cytokines including IL-12 (Duan et al., 2009; Eliopoulos et al., 2008; Gao et al., 2010), IL-21 (Hu et al., 2011), IL-24 (Zhang et al., 2013), TNF- α (Shahrokhi et al., 2013), and IFN- γ (Bitsika et al., 2012). TRAIL (tumor necrosis factor related apoptosis induced ligand) (Shahrokhi et al., 2013), nanoparticles (Gao et al., 2013) and anti-angiogenic factors (Ghaedi et al., 2011).

CANCER STEM CELLS AND VACCINES FOR CANCERS

All cells in a tumor mass are not the same type. A minor subset of cells in the tumor mass are considered to be responsible for facilitating tumor initiation and maintaining tumor growth (Chiba et al., 2006; Collins

et al., 2005; Patrawala et al., 2005). These cells are called cancer stem cells or cancer-initiating cells. Cancer stem cells are believed to be transformed from stem cells or progenitor cells, or converted from normal cells (Lobo et al., 2007). Cancer stem cells and normal stem cells share many traits, including the ability of self-renew, limited differentiation, enhanced mobility, and proliferation (Beier et al., 2007; Tinhofer et al., 2014).

Currently the three standard cancer treatment options are surgery, radiotherapy and chemotherapy. However, many patients receiving prolonged oncological treatment suffer from complications caused by adverse effects of these treatments. These patients may experience a poor quality of life and will often still relapse post-treatment (Goldfarb and Ben-Eliyahu, 2006; Nabholz et al., 1996; Valero et al., 1995). The main reason current treatment options fail is thought to be due to cancer stem cells, which cannot be eradicated by traditional treatment modalities. Cancer stem cells divide slowly and are resistant to drugs, therefore, CSCs have the ability to be resistant from radiation and conventional chemotherapy. Due to unlimited proliferation and increased motility, cancer stem cells are thought to give rise to the bulk of the tumor, to promote recurrence, and cause metastases. The cancer stem cell concept therefore implicates new approaches in the treatment of cancer, including specifically targeting cancer stem cells, instead of trying to solely reduce the tumor mass.

Normally the immune system is responsible for retrieving and clearing cancer cells from our body. However, studies have shown that cancer stem cells have the ability to evade the immune system (Schneider et al., 2011; Wei et al., 2010; Wu et al., 2010). Therefore, new cancer treatment therapy to target cancer stem cells by enhancing the immune system is important and necessary.

The process in which the immune system recognizes and kills cancer cells is dependent on the activation of antigen specific T cells by antigen presenting cells including dendritic cells, macrophages, and B cells. Since the discovery of dendritic cells (DCs) by Ralph Steinman in 1973 (Steinman and Cohn, 1973), DCs have been shown to perform as professional presenting cells, responsible for triggering an immune response.

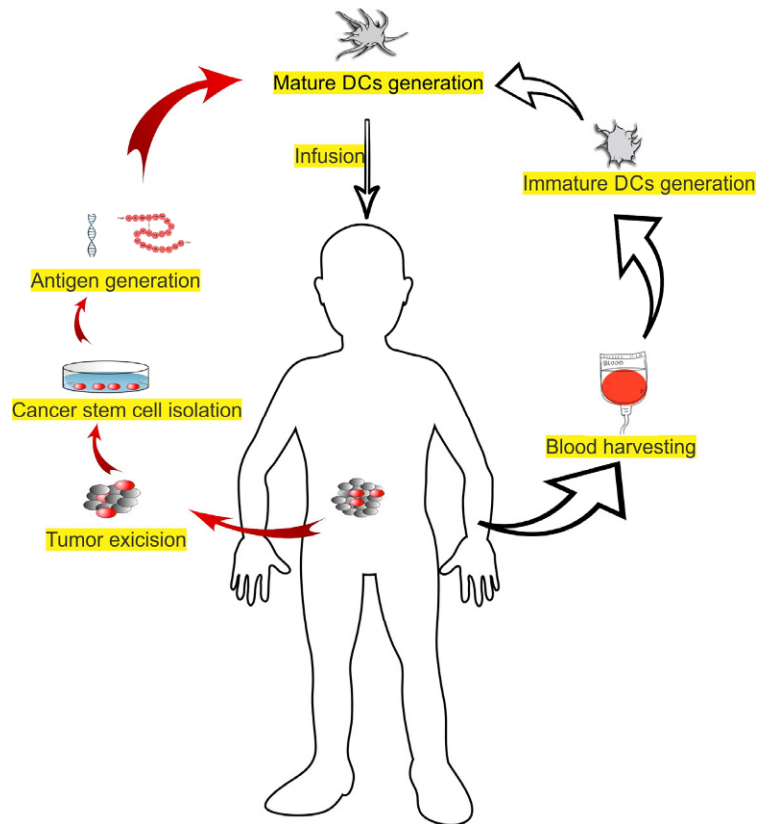


Figure 4. Cancer vaccination using cancer stem cell-derived antigen-primed dendritic cells. After the tumor is excised from the patient, cancer stem cells (CSCs) are isolated from tumor biopsy and used to generate CSCs-derived antigens or CSCs-derived mRNA. Meanwhile, immature dendritic cells (DCs) are generated from peripheral mononuclear cells blood, or from bone marrow cells. Then immature DCs are primed with CSCs-derived antigens or CSCs-derived mRNA to induce mature. DCs presenting CSCs-derived antigens are infused into patients to eradicate cancer stem cells.

Cancer treatments based on dendritic cells enhance the ability of the immune system to recognize CSCs through the presentation of surface antigens. CSCs carry specific-cancer glycans called CSC-markers, also known as CSC-associated antigens. Many efforts to load CSCs specific antigens onto dendritic cells have been performed. In cancer treatment using DCs, therapeutic DCs could be harvested from peripheral blood, or differentiated from peripheral blood-derived monocytes (Morse et al., 1997), or cultured bone marrow-derived stem cells (Bai et al., 2002). Recently DCs were generated from induced-pluripotent stem cells (Senju et al., 2011). DCs are then loaded with cancer antigens by various ways and reinfused into patient (Figure 4). Cancer antigens can be generated from tumor lysates (Yu et al., 2004), apoptotic bodies (Labarriere et al., 2002), peptides (Rosalia et al., 2013),

tumor RNAs (Kalady et al., 2004), and tumor-derived exosomes (Mahaweni et al., 2013). Cancer antigens could be loaded onto DCs by nano-sized carriers including nanoparticles or nanoemulsions (Park et al., 2013). Studies on mice have shown DCs primed by CSCs antigens effectively induced immune response to tumor cells and prolonged survival (Lu et al., 2015; Ning et al., 2012; Xu et al., 2009). Treatment with DCs loaded with CSCs-derived antigen induced a tumor-specific immune response stronger than that induced by DCs loaded with normal tumor cells (Dillman et al., 2012; Jachetti et al., 2013). Recently, clinical study on glioblastoma have shown that when patients were vaccinated with DCs transfected with mRNA derived from patient’s own CSCs, an immune response triggered by vaccination were identified. Compared to untreated patients, progression-free survival was 2.9

times longer in vaccinated patients (Vik-Mo et al., 2013).

CONCLUSION

Current research demonstrates a wide variety of ways engineered stem cells combat diseases like cancer. However, there are still many challenges facing stem cell therapies that remain to be solved. The number of adult stem cells in tissues is limited, and they are difficult to grow in the laboratory. Moreover, it is challenging to gain a sufficient number of adult stem cell types for clinical use. Fortunately, there are new ways to solve some of these problems. For instance, blood-forming stem cells make up a very small percentage of bone marrow. However, large amounts of whole bone marrow can be obtained and administered for transplantation in blood cancers. Another example is the use of adult stem cells, such as mesenchymal stem cells, that can be isolated from an individual and expanded in vitro. However, it is unclear if growing stem cells in the laboratory can induce any mutations that might cause disease later on. Some studies have shown MSCs promote cancer metastasis (Halpern, Kilbarger, & Lynch, 2011; Karnoub et al., 2007; Swamydas, Ricci, Rego, & Dréau, 2013). Another remaining issue is a rejection of transplanted stem cells. Host immune systems reject allogeneic stem cell transplantation and, therefore, require immunosuppressing drugs. Additionally, it can be difficult to find a donor whose human leukocyte antigens closely match the patients'. The recent discovery of reprogramming patient-derived cells has created a breakthrough in this field. Using these cells, known as iPSCs or induced pluripotent stem cells, eliminates the concern for rejection by the patient's immune system. iPSCs are also easy to grow, proliferate indefinitely and contain the broad potential to form many different cell types. One down side to using iPSC technology is in the process of reprogramming the cells. iPSCs are generated by insertion of genes by viruses into the cells chromosomes. This raises the risk of creating mutations that could transform stem cells into cancer cells. Further studies need to be performed to determine the long-term safety and efficacy of ex vivo expanded stem cells for use in engineering for cancer treatment. It also remains to be determined the optimal dose of engineered stem cells to have the therapeutic effect. There is no doubt that stem cell technology will play a big part in the future of cancer treatment.

However, as with any new technology, many issues need to be addressed prior to its widespread use.

ABBREVIATIONS

CSCs: Cancer stem cells; DC: dendritic cells; MSCs: Mesenchymal stem cells; SCT: stem cell transplant; iPSCs: induced pluripotent stem cells.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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