The Limitations and Solutions of Stem Cell Use in Cancer Treatments

Surabhi Bhaskar

Abstract

Stem cell therapy is an important treatment in the context of cancer. The use of embryonic stem cells in this field of study are controversial due to their origin from fetal cells and allogeneic stem cells have been a proposed alternative. While a preferred treatment, donor stem cells are accompanied by a host of issues, like graft-versus-host disease and rejection of the treatment. Due to recent advancements in the field, solutions to these problems are closer than ever. Radiation and chemotherapy are common therapeutic methods used to destroy cancerous cells and stem cells can be used to replenish the body with healthy cells. Stem cells can also be used as vehicles to carry chemotherapies to the tumor site. Chimeric antigen receptors (CARs) can be used to direct the stem cell transplant to the intended location and integrins can be used to contain them to that area. In order to prevent rejection of the graft by the host's immune system, certain proteins can be added and removed from the cell's surface through ex-vivo modification. Clinical trials have yielded promising results for these advancements in the treatment of cancers.

Discussion

Stem cells are the functional units that other cells of the body, such as blood and liver cells originate from. Through differentiation, stem cells become specialized adult cells or self-renew to maintain the pool of stem cells throughout the body. When a cell differentiates into an adult cell, it loses its potential to develop into any other type of cell that the body may require at a given moment. With this ability to produce various somatic cells, the development of a technique that takes advantage of stem cells to treat diseases and conditions has been a point of research for the past decades.

Regenerative medicine works to reproduce body tissue and organs in order to get them to function as they typically would. Researchers in this field of study have used stem cells to generate new, healthy cells to replace damaged adult cells. Burns, for example, are candidates for this treatment as skin cells have been destroyed by heat and stem cells can replenish the damaged tissue by supplying the body with new skin cells[1]. Due to donor organs being limited in supply, the development of stem cell therapy could prove to be a useful, more cost-effective alternative to organ transplants.

Sources of stem cells consist of embryos, adult tissue, amniotic fluid, and umbilical cord blood[2]. There are different types of stem cells, all with varying degrees of differentiation potential. Embryonic stem cells are extracted from blastocysts and are considered pluripotent, meaning that they can differentiate into a host of somatic cells[3]. This is opposed to cells taken from adult tissue where, although there are stem cells present in bone marrow or fat, adult stem cells are limited in number and in their ability to differentiate into cells other than those of the region they were taken from.

Totipotent cells, like zygotes formed from the fertilization of an egg by sperm, have the highest differentiation potential, meaning that cells can form embryonic and extraembryonic structures.

Totipotency enables these cells to develop into a germ layer or placenta, yet another plentiful source of pluripotent cells[4].

Despite having a wider potential for clinical use, embryonic stem cells are restricted by the donor cell being incompatible with the patient's immune system and the controversy surrounding their origin. The former can be addressed through therapeutic cloning where the nucleus of the recipient's somatic cell is transferred into the egg cell. This allows pluripotent cells taken from embryos to be accepted by the host's body instead of being rejected and attacked by the immune system[5]. However, this method is very expensive and relies heavily on available technologies. Additionally, it is not highly efficient as its yield is low. Moreover, the use of embryonic stem cells is controversial because they originate from human blastocysts only five to seven days old. In 2009, the National Institutes of Health established guidelines for human stem cell research to address the matter. Embryos created through in vitro fertilization are available for use when the embryo is not required by the egg or sperm donor and with informed consent from the individuals[6]. Still, some researchers have opted for a different approach to stem cell therapy that doesn't involve the use of embryonic cells.

More recently, there has been development on a method to revert specialized cells back into their pluripotent state. By taking a differentiated somatic cell–commonly a skin cell–and using specific transcription factors like the Oct4, Klf4, Sox2, and c-Myc proteins, researchers can control and change the behavior of the cell[7]. Induced pluripotent stem cells, due to their high cost, are more often used for drug testing and disease modeling as opposed to clinical treatment.

Tumor Tropism

As described above, stem cells are often acquired from a donor since the patient's damaged tissue cannot provide sufficient cells for the treatment. An example of this includes leukemia patients, whose bone marrow has been obstructed through chemotherapy or radiation directed at tumors of blood-forming tissues. Allogeneic transplants use donor cells to replenish the cells displaced by the cancer and destroyed by therapies to prevent metastasis.

The ability to grow and multiply at a rapid rate is part of what makes cancers such a destructive force. Chemotherapy targets this characteristic by administering drugs intravenously, orally, or topically to kill rapidly-dividing cells in the body by inhibiting their ability to divide and replicate their DNA. Stem cells can be used in conjunction with chemotherapy in order to deliver the treatment to the tumor site. Tumor tropism occurs when the tumor site induces chemoattraction of surrounding cells, often including stem cells[8]. While this is a detriment to the restoration process, it can be taken advantage of by using stem cells to carry a therapeutic drug, such as chemotherapy, to successfully deliver the treatment to the tumor site.

Mediating Graft-Versus-Host Disease

Complications of the immune system as a result of transplanted stem cells recognizing the host's body as foreign can develop following an allogeneic transplantation. This unintended off-target effect could be mediated by better controlling the localization of transplanted cells. This can be done with chimeric antigen receptors (CARs), which are proteins that can identify specific antigens. For instance, CD19 is an antigen expressed on all B-lymphocytes. T-cells, if

genetically modified to express anti-CD19 CARs (CAR19), will possess properties designed to combat any identified CD19+ target cells[9]. CD19 CARs are an example of modifying transplanted T-cells to target the CD19-expressing tumor and minimize off-target effects. This same concept could be applied with stem cell transplants to minimize off-target effects. This therapy has proven revolutionary in treating leukemias; however, it is limited by how costly the use of T-cells is and each transplant requires T-cells from the individual patient. This technology can be enhanced by instead utilizing stem cell-derived T-cells, which have been shown to minimize rejection of the transplant.

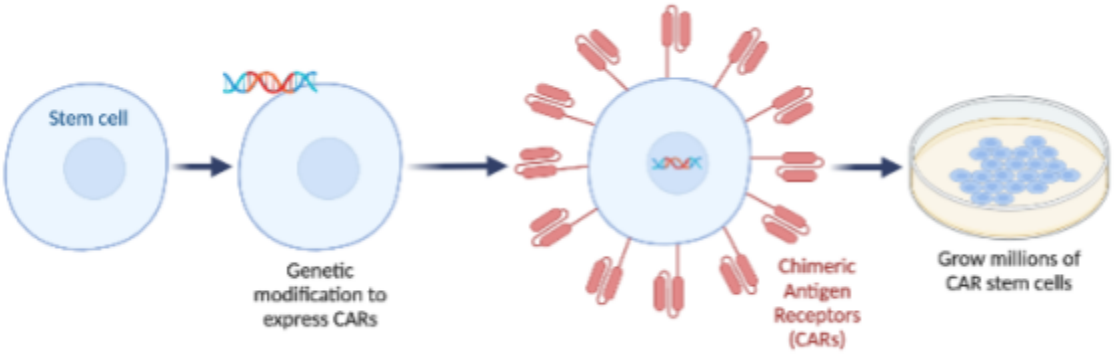

Fig. 1 | Adding CARs to stem cells. A stem cell is obtained and modified to express a gene that codes for CAR proteins. The modified CAR stem cell is then expanded to provide sufficient numbers for transplantation in order for the body to take up the graft. This will allow the cell to better target the tumor site as the CAR that is being expressed can identify an antigen specific to the tumor site. Created with BioRender.com

Another obstacle to overcome is retaining the stem cell treatment at the tumor site to minimize off-target damage. Integrins are receptors that regulate cell proliferation, survival, and motility–all vital to metastasis[10]. They can bind to extracellular matrix components (ECM) like ligands–ions or molecules bound to a metal atom–and cause outside-in signaling through which ECM molecules are able to bind to the receptor and take effect. Integrins can contribute to the progression of cancers and thus, being able to target integrins would minimize host damage. The most frequently studied integrins in cancer are αvβ3, αvβ5, α5β1, α6β4, α4β1 and αvβ6 because the tumor cell expression of these receptors are linked to disease progression in several types of tumors[11]. Since integrins correlate with the survival of the cell, integrins bound to ligands relay survival signals whereas unligated integrins promote apoptosis or programmed cell death. Tumors are characterized by their inability to perform apoptosis, leading to its uncontrollable growth. Therefore, by initiating integrin-mediated death, integrins can counteract their function of promoting cell growth and combat the tumor that it would otherwise allow to progress if ligated.

More pertinent to stem cell therapy, recent studies have shown overexpression of select integrins can increase retainment of stem cells in the desired location. In cardiac regeneration, a 25% improvement of cardiac performance post transplantation was reported when this method was used[12]. Through this method, modified stem cells that use integrins to keep them to specified locations can prevent off-target effects and enable the treatment to combat the tumor with greater precision. Since αvβ3, αvβ5, α5β1, α6β4, α4β1 and αvβ6 are important for tumor

progression, overexpressing these integrins can similarly boost retainment of stem cells to the tumor site.

Mediating Rejection of Stem Cells as a Cancer Treatment

When taking up an allogeneic treatment, there is a risk of the host's immune system recognizing the graft as a substance foreign to the body and attacking it. This is as opposed to syngeneic transplants in which identical genetic information is used. However, through ex-vivo modification of the allogeneic graft, the host's immune system can be surpassed. Gene editing allows for the creation of stem cell therapies that are universally immunocompatible and thereby will not face rejection by the host[8].

Human leukocyte antigens (HLA) are markers present on the surface of most cells of the body that allow the immune system to detect whether a cell is foreign or native to the host. By removing HLA proteins from the cells, the immune system would not detect the presence of foreign antigens. Then, the addition of PD-L1 and CD47 keeps macrophages from consuming cells that are not malignant, like the graft which may be mistaken as harmful[13]. HLA-E is added to make the cell appear normal despite its lack of a classified marker[14]. Killer Ig-like receptors (KIR) expressed on natural killer cells won't detect the absence of HLA proteins and will defer lysis.

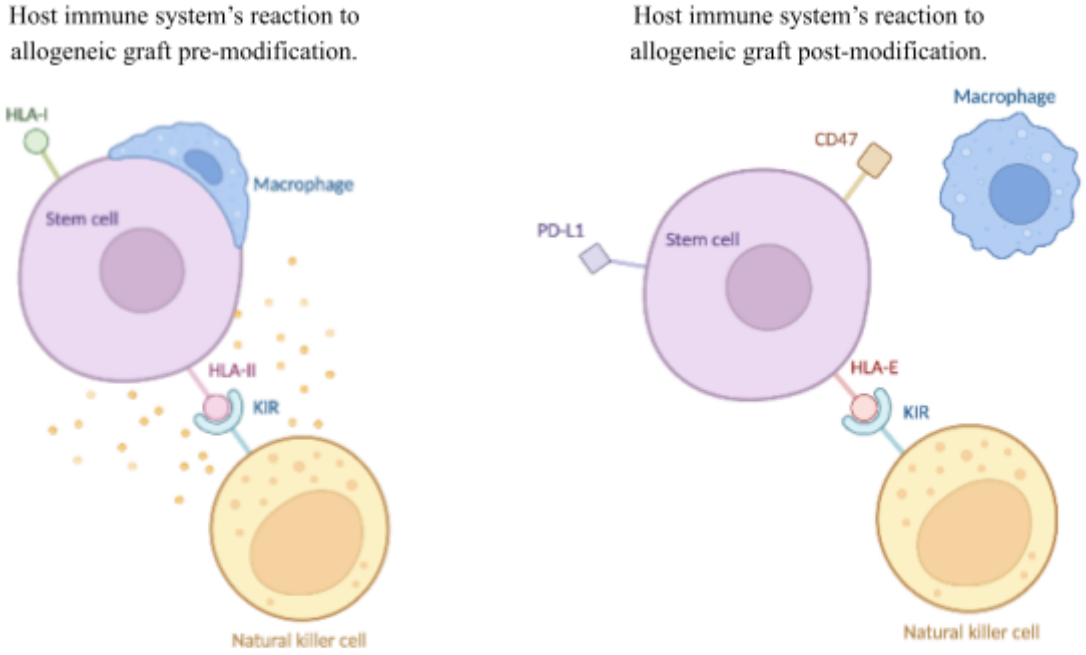

Fig. 2 | Rejection of the allogeneic graft. The immune system reaction when in contact with allogeneic stem cells without (left) and with (right) any external modification. The stem cell pre-modification will be recognized as foreign by NK cells when the HLA proteins on the stem cell bind to the KIR receptors on the NK cells. Then, NK cells will release cytotoxic granules that trigger lysis of the cell. By contrast, a modified stem cell will have the HLA-E protein which is a universal marker unlike HLA-I or HLA-II and therefore will not be identified as foreign to the body by the KIR receptor. This will not trigger the release of granules from the NK cell and will prevent cell death. Created with BioRender.com

Conclusion

Stem cell therapy is an evolving field of study. Its applications extend across a vast array of medical specialties, but in the context of cancer, there is a great deal of promise for effective treatment methods. The cost of replacing a failing organ entirely with a donor organ is expensive and time-consuming as the recipient is placed onto a waitlist amid other patients in varying circumstances. Stem cells, by comparison, have greater potential for convenient access. Due to controversy over embryonic stem cells, researchers are opting for the use of allogeneic hematopoietic transplants; however, they are not without their limitations. In order to curate the optimal course of treatment, it is imperative that any and all barriers are addressed. Such barriers in a successful treatment include rejection of the graft, off-target effects, and further metastasis of the tumor. These barriers can be addressed through gene editing such as CARs and integrins which are ex-vivo modifications to the stem cell.

In addition to obstacles present in the treatment itself, cost and accessibility are practical concerns that require attention. Despite the success T-cells harnessing CARs have in targeting specified B-lymphocyte antigens present on the surface of affected cells, it is an expensive source to tap into. Stem cells, on the other hand, are a much more cost-effective alternative as they can be reproduced in stem cells lines and have greater potential to be a more widespread treatment. Furthermore, as stem cells can be modified ex-vivo to be suitable for virtually any recipient, it is much more accessible than T-cell based therapies in which the cells need to be provided by the individual to prevent rejection of the graft.

References

1. Arno, Anna, et al. "Stem cell therapy: a new treatment for burns?." Pharmaceuticals 4.10 (2011): 1355-1380.
2. Bacakova, Lucie, et al. "Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells–a review." Biotechnology advances 36.4 (2018): 1111-1126.
3. Alikani, Mina, and Santiago Munné. "Nonviable human pre-implantation embryos as a source of stem cells for research and potential therapy." Stem Cell Reviews 1.4 (2005): 337-343.
4. Melo, L. G., C. A. Ward, and V. J. Dzau. "Gene therapies and stem cell therapies." J Cardiovasc Therap 3.3 (2007): 40-66.
5. Lisker, Rubén. "Ethical and legal issues in therapeutic cloning and the study of stem cells." Archives of medical research 34.6 (2003): 607-611.
6. Lo, Bernard, and Lindsay Parham. "Ethical issues in stem cell research." Endocrine reviews 30.3 (2009): 204-213.
7. Yamanaka, Shinya. "Induced pluripotent stem cells: past, present, and future." Cell stem cell 10.6 (2012): 678-684.
8. Kimbrel, Erin A., and Robert Lanza. "Next-generation stem cells—ushering in a new era of cell-based therapies." Nature Reviews Drug Discovery 19.7 (2020): 463-479.
9. Lee, Jung Min. "When CAR meets stem cells." International Journal of Molecular Sciences 20.8 (2019): 1825.
10. Seguin, Laetitia, et al. "Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance." Trends in cell biology 25.4 (2015): 234-240.
11. Desgrosellier, Jay S., and David A. Cheresh. "Integrins in cancer: biological implications and therapeutic opportunities." Nature Reviews Cancer 10.1 (2010): 9-22.
12. Lemcke, Heiko, et al. "Recent progress in stem cell modification for cardiac regeneration." Stem Cells International 2018 (2018).
13. Lanza, Robert, David W. Russell, and Andras Nagy. "Engineering universal cells that evade immune detection." Nature Reviews Immunology 19.12 (2019): 723-733.
14. Lee, Ni, et al. "HLA-E is a major ligand for the natural killer inhibitory receptor CD94/NKG2A." Proceedings of the National Academy of Sciences 95.9 (1998): 5199-5204.