“Mesenchymal and Induced Pluripotent Stem Cells: General Insights and Clinical Perspectives” (2015), by Helena D. Zomer, Antanásio S. Vidane, Natalia G. Gonçalves, and Carlos E. Ambrósio

In 2015, biologist Helena D. Zomer and colleagues published the review article “Mesenchymal and Induced Pluripotent Stem Cells: General Insights and Clinical Perspectives,” hereafter “Mesenchymal and Induced Pluripotent Stem Cells,” in Stem Cells and Cloning: Advances and Applications. The authors review the biology of three types of stem cells, embryonic stem cells, or ESCs, mesenchymal stem cells, or MSCs, and induced pluripotent stem cells, or iPS cells. Stem cells are a special cell type that can develop into any other type of cells and are essential for development. The authors specifically evaluate the potential applications of MSCs and iPS cells for regenerative medicine, or the field of medicine that focuses on developing methods to regrow or repair damaged cells, organs, or tissues. Zomer and colleagues assert that both MSCs and iPS cells have the potential to be used for a variety of applications in regenerative medicine.

The authors discuss pluripotent stem cells, which can divide and multiply indefinitely and are important within the embryonic phase since they can differentiate into many different kinds of cells in an organism. When pluripotent stem cells divide, the resulting cells can either remain as stem cells or differentiate into more mature, specialized cells. When a cell differentiates it gains characteristics of specific types of cells in the body. For example, if a stem cell differentiates into a liver cell, it gains the traits of cells in the liver to help process toxins from the blood. While pluripotent stem cells are able to differentiate into different types of cells, not all stem cells can. For example, stem cells found in certain structures in the adult body have a limited range of cells into which they differentiate. Unlike pluripotent embryonic stem cells, stem cells found in adults cannot turn into as many cell types. Stem cells that can only differentiate into a limited number of other kinds of cells, rather than any kind as pluripotent cells can, are called multipotent.

The authors of “Mesenchymal and Induced Pluripotent Stem Cells” all worked at the University of São Paulo in São Paulo, Brazil, in the Department of Veterinary Medicine and Animal Science. In 2015, Zomer and Natalia G. Gonçalves were both graduate students, Antanásio S. Vidane was a research professor, and Carlos E. Ambrósio was an associate professor. The authors were all involved with stem cell research.

Zomer and colleagues separate “Mesenchymal and Induced Pluripotent Stem Cells” into six major sections and an abstract. In the Abstract, they state their goal is to discuss the therapeutic advantages of both mesenchymal and induced pluripotent stem cells. In the “Introduction,” the authors provide operational definitions for the different types of stem cells. Then, they continue with examples of the similarities and differences between MSCs and iPS cells in “General Characteristics of Stem Cells.” In their next section, “MSC,” the authors further examine the benefits and disadvantages of using MSCs in certain types of research. Similarly, in their next section, “iPS cells,” the authors look at the advantages and disadvantages of iPS cells. In “Clinical Perspectives of Mesenchymal and iPS cells,” the authors describe the potential and actual uses of both MSCs and iPS cells in medical research. In the “Conclusion,” the authors give final thoughts on regenerative medicine stating that there is not enough information at the date of publication in 2015 to make a final decision as to which may be the best option for regenerative medicine.

In the “Abstract,” the authors describe the motivation behind their article. They start by assert-

ing that various researchers have been interested in studying regenerative medicine using MSCs. MSCs, they assert, are relatively easy to obtain in high amounts and have the ability to differentiate into other cell types. However, scientists had recently developed technology to create iPS cells, which have their own set of advantages and potential applications for regenerative medicine. The authors explain that both types of stem cells have great potential for future medical therapies, and that in their article they aim to discuss the therapeutic advantages and disadvantages of each.

In the "Introduction," the authors describe what they consider the foremost characteristics of stem cells, their capability for self-renewal and their plasticity. Self-renewal is the capability for stem cells to divide to create more stem cells, to replenish the stem cells, and to create further specialized cells. The scientific community disagrees on the definition of plasticity, but the authors define plasticity as the capacity to differentiate into specific mature cell types. They state that plasticity is one of the key factors that will determine whether a specific type of stem cell is important for regenerative medicine because of stem cells' potential to grow and regenerate tissues. Since there are many different classes of stem cells with many different capabilities, the high plasticity of iPS cells is what sets them apart.

Continuing in the "Introduction," the authors explain the sources of different types of stem cells. The first type of stem cells that the authors discuss are ESCs, which are isolated from blastocysts, or the cell mass during the early development of mammals. ESCs have very high plasticity, as the cells of blastocysts have not yet differentiated into any specialized cell type. However, ESCs are taken from human embryos, a practice that many people see as unethical. The authors also discuss MSCs, which are derived from less mature types of adult tissue such as bone marrow, liver, muscle, and fat tissues, and are less plastic than ESCs. Lastly, they discuss iPS cells, which are stem cells taken from mature adult tissue, but that scientists reprogram to be more plastic than other adult cells would be. The authors suggest that iPS cells may be able to replace ESCs in research because they can have equal levels of plasticity, and do not come from a controversial source.

In the next section, "General Characteristics of Stem Cells," the authors distinguish between different levels of potency and use them to categorize the stem cells they discuss. ESCs are pluripotent, as they have not developed into any specialized cell type and have the potential to differentiate into many different types. MSCs are multipotent, as they are already starting to specialize into a distinct cell type. Lastly, Zomer and colleagues discuss iPSs, which despite coming from adult tissue, scientists can induce to be pluripotent again. The authors note that other scientists had only recently developed the technology to create iPSs. Specifically, they mention Kazutoshi Takahashi and Shinya Yamanaka, who developed a process in 2006 that can take a differentiated mouse cell and make it into a pluripotent iPS cell. In 2007, their group used the process to revert human fibroblast cells to human iPS cells. Yamanaka won a Nobel Prize for Physiology or Medicine in 2012 along with developmental biologist, John B. Gurdon, for their reprogramming technology for iPSs.

Next, in the "MSC" section, the authors describe the potential uses of and barriers for the use of MSCs. The authors expand on the locations in the body where MSCs are located, listing the umbilical cord blood, placenta, and dental pulp, in the center of the tooth. Within the human body, MSCs produce cells that support organs and help regulate the flow of certain substances. The MSCs have the potential to differentiate into a variety of cells, including bone cells, fat cells, cartilage cells, and liver cells. MSCs are one of the most important cell types for regenerative medicine, and among all the different types of stem cells, scientists have studied MSCs the most and shown that they are generally safe to use for regenerative purposes. The ethical benefits for MSCs use include that there is minimal to no capacity for MSCs to cause tumors to grow upon transplanting, which they state is a common occurrence with other types of cell grafts. Human bone marrow cells, the most widely studied MSCs according to the authors, are invasive and expensive to obtain due to their location within bones. Zomer and colleagues acknowledge that the scientific community needs to find alternative sources of MSCs for future research, due to limited access to MSCs.

The following section titled "iPS cells" describes the advantages and drawbacks of iPSs. The authors remind that iPS cells are only possible because scientists learned how to alter certain genetic factors within an adult somatic cell. Zomer and colleagues detail that scientists can essentially reprogram adult cells by altering their genetics so the cells revert to a more primitive stage and have the same plasticity with potential to differentiate as an embryonic stem cell. The pluripotency of iPSs is so

similar to that of embryonic stem cells, that scientists can use iPSs to grow many kinds of cells and even embryonic structures. Although iPSs are similar in function to embryonic stem cells, the two cell types are not identical at every level. The authors note that, as of 2015, the reprogramming process of converting adult cells into iPS cells still was not very efficient and need to be improved upon. That means that, at least at the time of publication, there were still some factors that limited the viability of the technology.

The authors in "Clinical perspectives of mesenchymal and iPS cells" speculate on the uses and limitations of both MSCs and iPSs in scientific research. They explain that stem cells can promote growth and physical repair in injured tissues when therapeutically applied. Zomer and colleagues list several characteristics that make stem cells ideal, such as coming from an easily accessible source, having long-term survival, and being able to easily integrate into the host site. They also note that in therapies using MSC or iPS cells, scientists prefer an autologous transplant, meaning obtaining stem cells from the patient's own body to reduce risks of rejection. The immune system is designed to attack foreign cells or tissues, so cells from another person's body have a higher probability of being rejected during cell transplants.

In comparing MSCs to iPSs, the authors describe the advantages and disadvantages of both. They state that the benefits of MSCs include that they are easy to grow outside of the body and easy to graft into the body upon transplantation. Clinicians use MSCs for cancer therapies, wound healing, and in the regeneration of cardiac, liver, and kidney cells. However, the authors note that MSCs often lose plasticity quickly after being introduced. Additionally, they explain that invasive means are often required to obtain the MSCs and that the current methods of procuring such cells often yield a small number of harvested cells. Zomer and colleagues explain that iPS cells do not have those downsides. Those cells can often be procured by non-invasive means and have a higher potency and plasticity, making them more attractive for regenerative therapies according to the authors. The authors explain that scientists have tested iPS cells for nerve regeneration and synthetic tissue production with limited results, as the transplanted cells were often rejected in such trials. Despite some issues using iPS cells, the authors insist that research is advancing rapidly and that iPS cells still have high potential to be used in a wide array of therapies.

In the "Conclusion" section, the authors restate the advantages of both MSCs and iPSs cells. MSCs are easy to collect and maintain, and can quickly be used after they are cultured. On the other hand, iPS cells have wider possibilities of application in disease treatment because they are pluripotent. However, the authors state that more research into iPS cells is necessary to make any long-term conclusions about their potential therapeutic applications.

Since the article's publication 2015, other scientists have expanded on Zomer and colleagues' ideas in a variety of other articles. In 2017, a group of researchers suggested that applications of the cancer suppressing protein, p53, based on how stem cells like MSCs and iPSs preserve genomic integrity by keeping mutations very low. That means that scientists think they can learn more about how to activate and inactivate the p53 protein based on the life cycle of a stem cell. Another article from 2019 suggested that scientists may be able to use stem cells like iPS cells to create better options for regeneration of hair. As of 2021, scientists are continuing to research uses for MSCs and iPSs in a wide variety of regenerative medicine treatments. According to scientists Tomer Halevy and Achia Urbach, the use of iPS cells may quash previous ethical concerns of the use of embryonic stem cells since the two stem cell types function basically the same, and there is no need to destroy an embryo to procure iPS cells.

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