Induced Pluripotent Stem Cells: The Most Versatile Source for Stem Cell Therapy

Marcie A. Glicksman, PhD

Orig3n, Inc, Boston, Massachusetts

ABSTRACT

Cell therapy has existed since the first bone marrow transplant in the 1950s involving identical twins. The blood-forming stem cells were used to restore healthy blood cells for the twin with leukemia. It was not until 1968 that genetic matching (known as human leukocyte antigen matching) was known to be important, and not until 1973 that bone marrow transplants were performed from non–twin-related and nonrelated donors. The most important application of human stem cells is for the generation of cells and tissues for cell-based therapies. Currently, donated organs and tissues are often the only option to replace diseased, injured, or destroyed tissue. The availability for these transplantable tissues and organs is very limited, however. To satisfy the demand for a source for these cells and tissues, induced pluripotent stem cells that have been differentiated into specific cell types can serve as a renewable source of replacement cells and tissues. A bank of suitable human leukocyte antigen–matched cells will be an important source providing immediate availability of cells that are readily scalable, economical, and well characterized. Areas of active pursuit with stem cell therapy is being investigated for treating diseases such as macular degeneration, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, rheumatoid arthritis, and neurodegenerative diseases. This article describes the advantages and hurdles for the use of induced pluripotent cells as the starting material for a source of replacement cells for regenerative medicine. (*Clin Ther*. 2018;■:1–6)

Key Words: stem cells, cell therapy, induced pluripotent stem cells, regenerative medicine.

HISTORY OF THE USE OF STEM CELL THERAPY

Bone marrow transplantation in the 1950s was the first demonstration that cell therapy can be beneficial for replacing damaged cells and tissues. The blood-forming stem cells isolated from bone marrow from identical twins were used to restore healthy blood cells for the twin with leukemia. Dr. E. Donnall Thomas, a physician working in Seattle, later won the Nobel Prize for this work in 1990.[1] It was not until ~10 years after that first transplant, in 1968, that the importance of genetic matching (known as human leukocyte antigen [HLA] matching) was realized.[2] By 1973, bone marrow transplants were performed from non–twin-related and nonrelated donors. Today, bone marrow transplants are commonly used for when a patient needs to replace the blood-forming stem cells that have been damaged from disease, high doses of radiation, or anticancer drugs. The most serious risks from bone marrow transplantation include a high risk of infections that can last throughout the patient's life and a risk of graft-versus-host disease, which is caused by an incompatibility between the donor and the recipient's cells. The limitation is that bone marrow transplantation has only been established for replacement of blood cells. Bone marrow as a source of stem cells is classified as adult stem cells, which are found not only in adult tissues and organs but also in infants and children. They include hematopoietic stem cells, neural stem cells, and mesenchymal stem cells (MSCs). They are not pluripotent because they can only form the cells in the organ or tissue in which they are found. Adult stem cells must be harvested from tissues and expanded. The expansion to produce the number of

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cells needed is often a limitation to the utility of the process.

The next big advancement for cell therapy was by a team led by James Thomson at the University of Wisconsin, Madison, in 1998.[3] The Thomson group reported the creation of the first human embryonic stem cells that they isolated from early-stage human embryos. Embryonic stem cells were found to be pluripotent, meaning that with biological signals that are defined during development, they will differentiate in vitro to form any cells and tissues in the body. The use of embryonic stem cells at the beginning of the 21st century generated a lot of excitement but also elicited some ethical issues with restrictions on the use of embryos for the generation of embryonic stem cells.[4] In the United States, restrictions amounted to defining a limited number of established embryonic cell lines that were approved for research purposes. This action severely restricted the widespread use of embryonic stem cells for cell therapy. Accessing a source of embryonic stem cells is one of the main limitations, in addition to the ethical concerns.

To further advance the field of cell therapy, three independent groups, Shinya Yamanaka[5] in Japan in 2007, James Thomson in Wisconsin in 2007,[6] and George Q. Daley[7] in Boston in 2009, announced that they had created induced pluripotent stem (iPS) cells by reprogramming adult human cells. Initially, skin fibroblasts were used,[5,6] but then peripheral blood mononuclear cells[7] were also found to be a good source for generating iPS cells. The adult cells are induced by 4 transcription factors to form iPS cells. iPS cells provide the most versatile and readily available source of cells for regenerative medicine and cell therapy.[8] iPS cells are derived from adult cells, not embryos, and, therefore, there are no restrictions as to their use. They stably proliferate and serve as an unlimited source of cells. As with embryonic stem cells, iPS cells have unlimited proliferation potential, they are pluripotent, and they can be induced to differentiate to form >200 cell types in the body. Comparison between embryonic stem cells and iPS cells reveals generally similar gene expression and the same pluripotency potential.[9,10] Limitations include the time it takes to create stable iPS cell lines.

WHY DO STEM CELL THERAPIES OFFER SO MUCH PROMISE?

Adult stem cells have an inherent function in the body to repair and replenish the existing cells in our body and to stimulate growth of needed cells. This process is true for the adult stem cells that are found in most organs in the body; however, different numbers of stem cells are found in different tissues. The most prominent example is the skin, which must withstand daily insults from the environment. We replace the outer layer of our skin every 2 weeks and rely on the supply of adult stem cells that are stored below the skin.[11] In contrast, other organs, such as the heart, are found to have very few adult stem cells and, consequently, have very little regenerative and repair ability. Although adult stem cells are already present in some of our organs and tissues, there are not nearly enough of them for when a catastrophic illness or injury occurs that will require a greater number of adult stem cells than for repair and regeneration of the injured tissue.

Applications of exogenous stem cells can function multiple ways in regenerative medicine. Stem cells can replace the damaged cells with functioning healthy cells, a process called engraftment. Another possible way stem cells can stimulate growth and repair is with physical contact with the endogenous cells. This process has been explored by measuring and characterizing the proteins that stem cells secrete, sometimes referred to as the secretome.[12–15] Depending on the cell type, growth factors and anti-inflammatory molecules can be part of the secretome. For example, conditioned media from mesenchymal cells isolated from adipose tissue were collected and shown to have beneficial effects with increased viability on hepatocytes in vitro.[13] Exosomes are part of the secretome and consist of cell-derived lipid vesicles that can contain DNA, mRNA, microRNA, and protein.[14,16] Exosomes are present in cultured medium from cells and are released from the plasma membrane when vesicles fuse with the plasma membrane or directly from the plasma membrane itself. This field is a new and rapidly growing area of research, and exosomes are believed to have specialized functions in cell communication.[14] There is still much to be understood as far as the types of exosomes, their specialized function, and how their release may be controlled by multiple factors.

WHAT DO WE KNOW ABOUT HOW STEM CELLS CAN BE USED?

The stem cell most studied as a therapeutic in humans has been the MSC. MSCs are multipotent, meaning that they can form >1 type of differentiated cell but