An Update on the Frontlines of Alternatives to Embryonic Stem Cell Research

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Embryonic stem cell research remains a controversial area of regenerative medicine, a field of medicine investigating means of repairing damaged or destroyed cells, tissues, and organs. While much hope and promise has been placed in the success of embryonic stem cell (ESC) research, only two clinical trials utilizing embryonic stem cells have been approved by the FDA. Those initial trials will examine the safety of using those cells in humans. Even though ESC research receives much of the public attention directed towards regenerative medicine, other areas of research, including adult stem cell research and cell reprogramming are steadily progressing. Unlike ESC research, no significant ethical issues surround these two avenues of research. While not without their challenges, adult stem cells and cell reprogramming offer two ethical and promising alternatives to ESC research.

Adult Stem Cells

Adult stem cells are unspecialized cells that can be found in several organs and tissues in the human body including the liver, heart, skin, and brain. Due to the difficulty of isolating and harvesting stem cells safely and efficiently from those tissues, adult stem cell research has focused on populations of stem cells that can be easily obtained including stem cells found in the peripheral blood, bone marrow, umbilical cord, amniotic fluid, and placenta. Stem cells taken from the bone marrow have been routinely used to treat leukemia, hemopathies, and blood disorders for more than 40 years. Bone marrow contains two populations of stem cells: hematopoietic stem cells (forms white and red blood cells) and mesenchymal stem cells (form bone, cartilage, fat, and other cells). So far, the majority of clinical treatments have utilized blood and bone marrow derived stem cells. To date, over 70 diseases and conditions have been treated with adult stem cells.

Umbilical Cord Stem Cells

The umbilical cord appears to be a particularly advantageous source of adult stem cells, as it contains a rich and non-invasive source of stem cells that can be easily obtained. Like bone marrow, the umbilical cord contains two separate sources of stem cells, hematopoietic stem cells taken from the cord blood and mesenchymal stem cells isolated from the Wharton's jelly. Umbilical cord blood has been used in stem cell transplantations for approximately 20 years. Cord blood stem cells have been used to treat approximately 80 diseases including both malignant and non-malignant diseases. Mesenchymal stem cells isolated from the umbilical cord have been found to differentiate into cell types outside of their lineage including neurons and cardiac muscle increasing their clinical potential. Stem cells isolated from the umbilical cord have certain clinical advantages over cell populations including a reduced risk of viral contamination and lower risk of graft versus host disease. Additionally, partial human leukocyte antigen (HLA) mismatches are well tolerated by transplant patients, a particular issue with bone marrow transplants. One disadvantage to umbilical cord hematopoietic stem cells is the limited number of stem cells that are produced per cord blood unit. Ex vivo expansion techniques are being explored with some success. A recent study, for example, successfully expanded and transplanted cord blood stem cells in leukemia patients. Mesenchymal stem cells isolated from the umbilical cord can be efficiently expanded ex vivo allowing enough stem cells to be generated for clinical applications. Stem Cell Reprogramming

Cell reprogramming is the process of converting one cell type into another type. Two methods of cell reprogramming are currently being investigated by scientists, induced pluripotency and direct cell reprogramming. Both methods are still in the research stage of development and have not been tested as a treatment in humans. Further research is needed to determine if induced pluripotent stem cells or directly reprogrammed cells will be useful as clinical treatments.

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPS) are fully differentiated cells that have been reprogrammed into cells that have embryonic stem cell-like properties, specifically pluripotency. This process is known as dedifferentiation. In 2007, two separate proof-of-principle studies were published demonstrating the ability of turning human somatic cells (adult cells found in the body other than egg and sperm germ line) into pluripotent cells through the reprogramming of certain genes. iPS cells could theoretically be created from skin cells biopsied from patients and used to treat the patient without the threat of immune rejection. iPS cells have already been used to create a library of stem cells lines from skin cells taken from patients with a number of different diseases including Parkinson disease, type 1 diabetes, Duchenne muscular dystrophy, and Huntington disease. These cell lines may help scientists to better understand the pathology of these particular diseases as well as test new treatments. Additionally, in mouse models, iPS cells have been used to correct sickle cell anemia demonstrating their usefulness for stem cell therapy.

Recently, adult mice have been generated from induced pluripotent stem cells. This was an important step to demonstrate that iPS cells have complete pluripotency, meaning they can differentiate into all cell types in an organism. Without proper safeguards, however, this technique could theoretically be used to clone humans, although the complexity of the human species may prevent this. Scientists are investigating how well iPS cells differentiate into particular cell types, an important step to determine their clinical potential. The pluripotency nature of iPS cells makes these cell subject to similar issues of ESCs including problems with the development of tumors, which may ultimately prevent these cells from being useful as a cell replacement therapy.

Cell Direct Reprogramming

Direct cell reprogramming or direct conversion (also referred to as transdifferentiation) occurs when a differentiated cell is reprogrammed to a different cell type without first being reversed to a pluripotent state. Four examples have been demonstrated so far. In 2008, Douglas A. Melton’s lab demonstrated this technique in mice by reprogramming pancreatic exocrine cells to insulin-secreting beta cells of the endocrine portion of the pancreas.1 In 2010, Marlis Wernig’s lab reprogrammed mouse fibroblasts into neurons and Deepak Srivastava’s lab reprogrammed cardiac and dental fibroblasts into cardiac muscle cells.2 A recent study from Gigue Bhatia’s lab became the first to demonstrate that this technique can be applied to human cells, converting dental fibroblasts into blood progenitor cells. These progenitor cells in turn produce functional cells from all three classes of blood cells (white blood cells, red blood cells, and platelets).2 Clinical trials using directly converted blood cells could begin as early as 2012. This technique appears to be more efficient than iPS cells. In experiments, up to 20% of cells were successfully reprogrammed. In contrast, iPS cell reprogramming has an efficiency of less than 0.1%. Directly reprogramming one cell type to another occurs in a shorter period of time, an additional advantage over iPS cells. In terms of clinical application, these cells may have a lower risk of tumor formation due to their lack of pluripotency and would also avoid issues of immune rejection. The cells could be taken from the patient’s DNA, directly or potentially be reprogrammed in vivo. Unlike iPS cells, directly converted cells do not multiply easily in the lab, limiting their usefulness for applications that require large amounts of cells, such as drug screening. Further research is needed to determine if these cells will effectively work as a cell replacement therapy and if there are any issues with epigenetic modifications (changes that alter gene expression, but do not the DNA sequence). Like iPS cells, these directly converted cells may help in the screening of new medications and in the study of disease pathology.

References

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3 See, for example the list of diseases treated at the New York Blood Center National Cord Blood Program available at http://www.nationalcordbloodprogram.org/epi (accessed December 8, 2010).
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