Science Highlights

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The State of the Stem Cell

Too many choices?

The big question facing scientists is: what type of pluripotent stem cell will ultimately prove to be the most therapeutically valuable?

As we enter a new decade of this new millennium, stem cell science is in a state of confusion. The power of pluripotent stem cells to alleviate damage to organs has been amply demonstrated in many model systems (1). It is not hype to assert that pluripotent stem cells are the foundation upon which regenerative medicine will grow. The over arching problem now, however, is lack of consensus about which stem cells to use and how to use them.

Simply put, the big question facing scientists is: what type of pluripotent stem cell will ultimately prove to be the most therapeutically valuable? This report on the state of the stem cell outlines the choices, the concerns, and the unknowns, for each candidate therapeutic stem cell.

Egg-derived stem cells

Embryonic stem cells derived from discarded human embryos, and parthenote stem cells derived from artificially activated, unfertilized human eggs, are undeniably the most robust and stable cells currently known. Once we learned the

laboratory conditions necessary to support these remarkable cells, they have proven to multiply endlessly, maintain the integrity of their chromosomes, and retain through many, many cell divisions, the capacity to develop into all the tissues of the body. This is not surprising given that the purpose of the fertilized egg is to give rise to cells that can multiply rapidly enough to signal the mother to conserve the lining of her uterus in order to nourish the embryo, and ultimately all the tissues and organs that comprise a fetus (2,3).

Somewhat surprisingly, an unfertilized, artificially activated egg (a parthenote) also has the capacity to give rise to cells that can multiply rapidly and give rise to all the

same types of cells, but they do not organize themselves into a fetus. Sperm are needed for the higher order organization required to form functioning organs and a viable fetus. Many studies in animal models have demonstrated the value of injecting embryonic or parthenote stem cells into animals with diseased hearts or kidneys or injuries, such as spinal cord injury (1). In some instances it appears the embryonic stem cells differentiate into the cell type that needs to be replaced, in other instances, the mere presence of the stem cells themselves appears to support repair and regeneration of the injured or diseased cells and tissue.

Why are egg-derived stem cells not yet available for treatments of human diseases? The answer is partly medical and partly social.

Medically, the same tissue match needed for a blood transfusion or a kidney or liver transplant applies to stem cell therapies. Tissues are comprised of individual cells, bonded together in specific ways. The surface of cells is a protein matrix, unique to each person. To protect us from bacterial and virus infections, immune cells that circulate through our bodies by the trillions each hour are looking for foreign proteins. Such proteins are ruthlessly attacked and destroyed. The same thing happens to foreign kidneys and stem cells. So, in the absence of patient-specific stem cells, each individual would have to be matched to a specific type of stem cell. Theoretically, it is possible to create embryonic and parthenote stem cell banks that would contain lines of stem cells to match most people, analogous to present day blood banks. This could alleviate the need for patient-specific stem cells for chronic diseases, but the need to conduct a tissue match rules out the use of banked stem cells for emergency treatments. Moreover, since perfect matches are rare, individuals undergoing therapy with banked stem cells would need suppression of their immune system to keep the engrafted stem cells alive. This problem would be overcome by having everyone tissue-matched early in life, analogous to being blood-typed, or by having patient-specific stem cells banked for everyone -- both enormous, but not impossible, undertakings.

The possibility of creating embryonic and parthenote stem cell banks for therapeutic use has been derailed more by social considerations than by science. Concerns about the destruction of discarded embryos, or women donating eggs for scientific and therapeutic uses instead of procreation, have occupied thousands of hours of air time and created new careers for religious and medical ethicists.

Thus, many scientists and clinicians initially focused on developing clinical approaches with embryonic or parthenote stem cells have changed their research focus and sought more pragmatic sources of stem cells.

Other sources of stem cells

Stem cell therapy is, in fact, not new. There are stem cells in our bone marrow that give rise to all the types of cells in our blood stream, both red cells and white cells. The bone marrow stem cells produces billions

and billions of blood cells daily, and can entirely re-populate the bone marrow of a patient undergoing bone marrow transplantation to treat various cancers and anemias (3). Bone marrow stem cells have been studied for many years, but to date, laboratory conditions have not been found that support their cell division in the same robust way embryonic and parthenote stem cells multiply. As a consequence, there are currently not enough bone marrow stem cells available for all the folks who need them for proven therapeutic uses, leaving very few for experimental stem cell therapies. Moreover, most studies reveal they lack the versatility of egg-derived stem cells. They can become all the cells in blood, but do not become all the cell types in the body. Nonetheless, some scientists and clinicians have abandoned their work with stem cells derived from eggs, and turned to trying to adapt bone marrow stem cells to laboratory conditions that will support their endless multiplication and subsequent development into all the tissues in the body. Once they succeed, bone marrow stem cells will still need to be tissue-matched to the patient.

Another source of stem cells already in clinical practice for stem cell therapy is umbilical cord blood. These cells can be recovered from the umbilical cord and placenta of every baby that is delivered. They, too, have been studied for many years (3) and, like bone marrow stem cells, laboratory conditions have not been found that support their cell multiplication to the numbers needed for therapies for adults. At this time, umbilical cord blood treatments are limited to treatment of children because there are not enough cells to treat adults. Tissue matching is also needed. Nonetheless, some scientists and clinicians have focused their research efforts on stem cells derived from umbilical cord blood.

Many other sources of stem cells have also been reported, such as stem cells from fat pads, placentas, amniotic fluid, roots of teeth and hair follicles, and are currently being characterized.

Induced pluripotent stem cells

Discovered by Shinya Yamanaka, MD, PhD at Japan's Kyoto University in 2007, these new stem cells give rise to a totally new category of pluripotent stem cell. "Yamanaka screened 24 candidate proteins before finding four that were able to reprogram adult cells, reverting them to their embryonic state. He and others then showed that these factors are also effective in human cells. Developmental biologist James Thomson, of the University of Wisconsin was the first to identify a slightly different group of factors that do the same." - Ian Wilmut, Time, April '08

In the midst of this research melee, a Japanese team reported that ordinary cells, fibroblasts, cultured from small skin biopsies, could be manipulated in the laboratory to behave similarly to egg-derived stem cells (1). This was accomplished by changing the expression of a specific, small set of genes in the cells (link to iPS cartoon). After a few weeks, the new type of cell, termed “induced pluripotent stem cell” seemed to multiply as rapidly as egg-derived stem cells, and

retain the capacity to differentiate into all cell types. The news rocked the stem cell scientific community. This could be the sought after source of patient-specific stem cells for therapies that would not require a tissue match or suppressing the immune system. The problem is that the manipulation to gene expression takes several weeks and resulted in some induced pluripotent stem cells that behaved like cancer cells. The formation of cancerous tumors if used therapeutically remains the major unknown for these iPS cells at this time.

Which stem cell will be the best for therapy?

The result of the many sources of stem cells is the current chaos. There are only a few thousand stem cell scientists in the world, and to develop therapies it is essential to pick a cell type and stick with it for the several years it will take to test safety and efficacy and qualify for treatments in humans.

The big question facing scientists: what type of pluripotent cell will ultimately prove to be the most therapeutically valuable? Value will be measured by alleviation of disease, and the absence of side effects, such as the growth of tumors.

Stem cells from testis

And in the midst of it all, a German research team quietly reported the derivation of stem cells from adult human testis. Like bone marrow, it is clear there is a large reservoir of stem cells in the testis because men produce billions of sperm each day throughout their lives. But most studies indicated the testis stem cells were restricted to giving rise solely to sperm. Now, however, two other research teams have derived stem cells from testis that so far behave like egg-derived stem cells. No manipulation of gene expression is needed and the cells multiply stably for many generations. Could this be the sought after patient-specific stem cell for therapeutic purposes? As of this writing, it is not clear how many stem cell scientists have diverted their research efforts to focus on testis-derived stem cells.

Bedford Stem Cell Research Foundation goals for 2010

The frustration at the lack of progress in patient-specific stem cell therapies is high at BSCRF, and we hope to end 2010 with successful derivation of several new patient-specific stem cell lines. Patient-specific stem cells will alleviate one of the barriers to moving therapies forward because they will be tissue matched, avoiding the need for immune suppression. Although depending on patient-specific stem cells for therapeutic purposes is deemed by many to be impractical because of the effort needed to establish each line, characterize it for safety, and prove efficacy, the relevant parameters have not been established. BSCRF scientists will begin in 2010.

Patient-specific parthenote stem cells

BSCRF scientists are halfway through the analysis of expression of all the genes turned on and turned off in the cells of 8-Cell human embryos. This stage of

development was chosen for study because the cells are totipotent (can give rise to all the cells in the body plus the placenta), and it is the stage at which the parthenote stem cells frequently arrest in culture. The goal is to increase the efficiency of deriving parthenote stem cells to at least 20% of artificially activated eggs, ensuring the derivation of a stable line of stem cells every time a woman undergoes an egg collection.

To date, several previously unknown and surprising characteristics of totipotent cells have been discovered and reported by BSCRF scientists, including possible control of cell division by an internal circadian clock. The work is ongoing.

Patient-specific testis stem cells

In parallel with this ongoing gene expression analyses, BSCRF scientists will establish in 2010 the efficiency with which stem cells can be derived from testis. Reports from some laboratories are as low as 5%, from others as high as 80%. The success rates from mouse testis in the BSCRF lab are currently 75%.

Testis biopsies are a routine procedure for infertility treatment, and there is a large body of medical evidence that there are few negative side effects from the procedure. The goal will be to determine the cost and speed of deriving patient-specific testis stem cells from normal men and from men with specific diseases such as spinal cord injury, diabetes, Parkinson's disease, ALS, heart failure and HIV infection. Three groups of trials with three men each are currently planned for 2010, beginning in April. The projected budget for each derivation and characterization is $35,000, $105,000 per group of three, $315,000 for the three groups.

The future

Although it appears costly at first, the rising cost of health care suggests patient-specific stem cell therapies for chronic, expensive diseases may ultimately lessen treatment costs. Parthenote stem cell research cannot be federally funded, even in 2010. The moratorium on parthenote stem cell research was not lifted by President Obama's executive order. The testis stem cell work might be federally funded, but such funding would create a need for BSCRF to put in place the costly and elaborate accounting practices needed during the Bush administration to separate federally funded projects from privately funded projects. To avoid this, federal funds will not be sought in 2010.

Once derived, the stem cell lines require six to twelve months to characterize for safety and potential to differentiate into the cell types needed for therapy. Given the ongoing work throughout the world to develop therapeutic approaches for stem cell delivery, 2011 may see the dawn of a new era in regenerative medicine.

(1) ILAR Journal (51) Jan, 2010 Regenerative Medicine: From Mice to Men. dels.nas.edu/ilar_n/ilarjournal/51_1/html/
(2) What is an Embryo? Connecticut Law Review, 2004.
(3) Human Embryonic Stem Cells, 2007, Jones and Bartlett.