Promises of Stem Cell Research and Therapeutics

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Introduction

Stem cells are smart cells of the body. It is the origin of life. As stated by the great pathologist Rudolf Virchow, "All cells come from cells." Today it is proved with evidence that all cells come from stem cells. The stem cells are derived from embryo, fetal tissues, and adult organs. Explicitly, stem cells can generate daughter cells identical to their mother (self-renewal), and under certain physiologic or experimental condition, depending on the source, they can differentiate into any type of cells such as heart muscle cells, blood cells, or the insulin-producing cells of the pancreas (differentiated cells). As the plant leaves flourishes from the stem, the body nourishes from the stem cells resting in our body. A more complete description of a stem cell includes a consideration of replication capacity, clonality, and potency. Thus, stem cells are considered to be unique cells with special attributes. It is these special attributes that offer the vast potential serving as a repair system of the body. Ever since the discovery of stem cells [1–5], scientists have dreamed of using them to repair damaged tissue or create new organs and has revolutionized the field of medicine.

This chapter will thus, introduce stem cells, the history of stem cell research and its promises in the field of regenerative medicine.

Stem Cell Backgrounder

Aristotle deduced that the embryo was derived from the mother's menstrual blood. The hypothesis that life did not arise spontaneously, but rather only from preexisting life (*omne vivum ex vivo*) was pronounced by Leydig in 1855. Virchow (1855) then extended this to postulate that all cells in an organism are derived from preexisting cells (*omnis cellula e cellula*), the fertilized egg. According to the principles derived from Leydig, Virchow, and Pasteur, life as we know it neither ends nor begins but is continuous. The adult human, for example, is only one stage in the cycle of human life (Fig. 1) [6].

Thus, during early embryonic development, each stem cell divides and gives rise to two daughter cells with the same potential, which is called symmetric division, whereas during normal tissue renewal in the adult, each stem/progenitor cell gives rise to one daughter cell that remains a stem/progenitor cell and one daughter cell that begins the process of determination

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I. Somasundaram (ed.), *Stem Cell Therapy for Organ Failure*,
DOI 10.1007/978-81-322-2110-4_1, © Springer India 2014

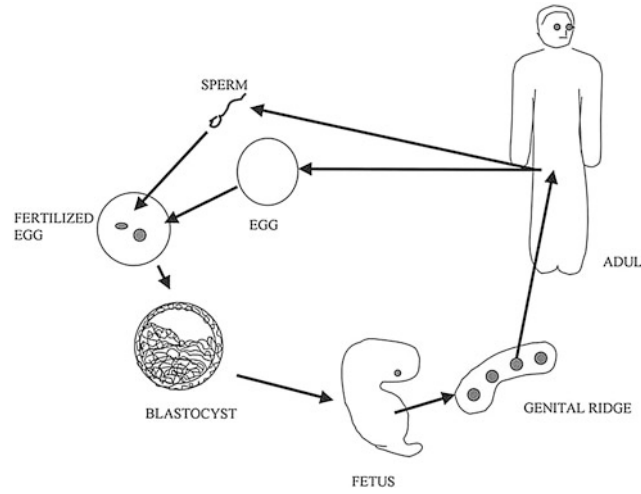

Fig. 1 Cycle of life. The life of an individual begins with formation of a fetus. Totipotent cells in the developing fetus migrate to the genital ridge and in adults produce germinal stem cells in the gonads. Germinal cells give rise to gametes (egg and sperm), resulting in cells containing half the chromosomes of an adult. Genetic reconstitution occurs when the sperm fertilizes the egg. Thus, life is continuous

to a terminally differentiated cell, which is called asymmetric division. The number of cells increases exponentially during early embryogenesis, but the cell number remains constant during normal tissue renewal, as the number of new stem/progenitor cells equals the number of cells destined to die.

History of Stem Cells from the Scratch

The potential of stem cells to revolutionize medicine got a huge boost with the emergence of adult stem cells. This timeline takes us through the ups and downs of the stem cell rollercoaster. The history of stem cell research started in the beginning of 1800s with the discovery that some cells could generate other cells. In the early 1900s, the first real stem cells were discovered when it was found that some cells generate blood cells. Research into adult stem cells in animals and in humans has been ongoing since this time, and bone marrow transplants – actually a transplant of adult stem cells – have in fact been used in patients receiving radiations and chemotherapy since the 1950s [7].

In 1973, a team of physicians performed the first unrelated bone marrow transplant. It required seven transplants to be successful. The 1990s saw rapid expansion and success of the National Marrow Donor Program (NMDP) with more than 38,000 transplants to date for the treatment of immunodeficiency and leukemia [8]. Developments in biotechnology in the 1980s and 1990s saw the introduction of first identity of embryonic stem cells and cloning by Martin Evans and Ian Wilmut, respectively [9–11], which paved way for targeting and altering genetic material and methods for growing human cells in the laboratory. These advances really launched stem cell research into the limelight, establishing the world's first human embryonic stem cell line which still exists today [12].

In the same year, John Gearhart (Johns Hopkins University) derived germ cells from cells in fetal gonadal tissue (primordial germ cells). Pluripotent stem cell "lines" were developed from both sources. The blastocysts used for human stem cell research typically come from in vitro fertilization (IVF) procedures. Since this discovery, a plethora of evidence has emerged to suggest that these embryonic stem cells are capable of becoming almost any of the specialized cells in the body and therefore have the potential to generate replacement cells for a broad array of tissues and organs such as the heart [13–15], liver [16,17], pancreas [18,19], and nervous system [20–22].

Progress in stem cell research is now astounding, with over 21,193 research papers on embryonic, iPS cells and adult stem cells being published globally in the year 2012 (Source:

Stem Cell Research: Trends and perspectives on the evolving international landscape. 2013 Elsevier B.V). Embryonic stem cells are still in its infancy in clinics with only 20 reported clinical trials till now; however, adult stem cells are already being used in treatments for over 4,000 clinical trials till date for a number of conditions including spinal cord injury, liver cirrhosis, neurodegenerative diseases, leukemia, cardiac problems, and so on (results from A service of the U.S. National Institutes of Health: clinicaltrials.gov).

Timeline of Stem Cell Research

1956	First successful bone marrow transplant between a related donor and recipient is performed by Dr E Donnall Thomas in New York. The patient, who has leukemia, is given radiotherapy and then treated with healthy bone marrow from an identical twin [7].
1958	Human histocompatibility antigens – Dausset discovers the first human leukocyte antigen [23].
1961	James Till and Ernest McCulloch first published evidence of the existence of stem cells in mouse bone marrow, a population of clonogenic bone marrow (BM) cells was found to generate myeloerythroid colonies in the spleens of lethally irradiated hosts [24].
1968	First bone marrow transplant for noncancer treatment. Dr Robert Good uses a bone marrow transplant to treat an 8-year-old boy with severe combined immunodeficiency syndrome (SCID). The donor is an HLA-matched sister (http://www.fhcrc.org/en/treatment/long-term-follow-up/FAQs/transplantation.html).
1970	Friedenstein and colleagues were the first to report that the rodent bone marrow had fibroblastoid cells, capable of forming colonies on plastic, which was later called a "mesenchymal stem cell" or MSC [25].
1973	First bone marrow transplant between unrelated patients. A 5-year-old SCID patient in New York treated with multiple infusions of bone marrow from a donor in Denmark (http://www.fhcrc.org/en/treatment/long-term-followup/FAQs/transplantation.html).
1978	The first IVF baby is born in England [26].
	Blood stem cells are discovered in human umbilical cord blood [27].
1981	Mouse embryonic stem cells are derived for the first time from the inner cell mass of a mouse blastocyst and grown in vitro [9,10].
1984–1988	Isolated pluripotent cell line of human testicular teratocarcinoma [28], a first example of clonal human embryonal carcinoma cells. When exposed to retinoic acid, these cells differentiate into neuron-like cells and other cell types [29, 30].
1987	National Marrow Donor Program (NMDP) and its Be The Match Registry initiated [31].
1989	Preimplantation genetic diagnosis (PGD) is developed – a method where a single stem cell can be removed from an IVF embryo and tested for inherited diseases. A clonal line of human embryonal carcinoma cells is derived that yields tissues from all three primary germ layers. They have limited replicative and differentiative capacity [32].
1990	Dr Thomas receives the Nobel Prize in Physiology or Medicine for his pioneering work on bone marrow transplants (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1990/).
1992	The first direct evidence of nervous system stem cells came from the identification and isolation of rat neural crest stem cells, clonogenic precursors that give rise to all known neural crest cell types, while self-renewing the neural crest progenitors [33].
1995	Scientists at the University of Wisconsin derive the first embryonic stem cells from nonhuman primates. These cells were reported pluripotent [34].
1996	The first organism ever to be cloned from adult cells is Dolly [11].
1997	Leukemia is shown to originate from a hematopoietic stem cell, the first direct evidence for cancer stem cells [35].
1998	Scientists at the University of Wisconsin, led by James Thompson, isolate and grow the first stem cells from human embryos. The embryos used in these studies were created by IVF [12].
	John Gearhart at Johns Hopkins University derived pluripotent germ cells from cells in fetal gonadal tissue (primordial germ cells) [36].

(continued)

2000	Scientists derive human ES cells from the inner cell mass of blastocysts. They proliferate in vitro for a long time and form all three germ layers and teratomas when injected into immunodeficient mice [37].
	Retinal stem cells (RSCs) isolated from the pigmented ciliary epithelium (CE) of the mouse and differentiate into retinal-specific cell types, including rod photoreceptors, bipolar neurons, and Müller glia [38].
2001	US president George W. Bush prohibits federal funding of research on human embryonic stem cells. The president claims that more than 60 stem cell lines are available for funding (http://georgewbushwhitehouse.archives.gov/news/releases/2001/08/20010809-2.html).
2003	Rare human breast cancer stem cells were identified and isolated [39].
	Cancer stem cells isolated in human brain tumors [40].
2004	California becomes the first state in the USA to provide its own fund for embryonic stem cell research (http://www.cirm.ca.gov/pdf/prop71.pdf).
2005	George W. Bush's restrictions on embryonic stem cell research are loosened (http://query.nytimes.com/gst/fullpage.html?res=9A01E0DE113FF93AA15754C0A9639C8B63&\penalty-\@Msec=health).
	Ernest McCulloch and James Till won the prestigious Albert Lasker Basic Medical Research Award, for first setting stage for all current research on adult and embryonic stem cells (http://laskerfoundation.org/awards/2005_b_description.htm).
2006	Induced pluripotent stem cells from mouse fibroblast cells by defined factors were generated [41].
2007	Evans shares the Nobel prize for medicine with Mario Capecchi and Oliver Smithies for their work on genetics and embryonic stem cells (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2007/).
	Induced pluripotent stem cells from adult fibroblast cells identified [42,43].
	Researchers at Wake Forest University and Harvard University report that stem cells drawn from amniotic fluid donated by pregnant women hold much the same promise as embryonic stem cells [44].
2008	Robert Lanza and colleagues at Advanced Cell Technology create the first human embryonic stem cells lines created without destruction of the embryo [45].
	First trachea transplant using woman's own stem cells [46].
2009	President Barack Obama lifts 2001 restrictions on federal funding for human embryonic stem cell research (http://www.gpo.gov/fdsys/pkg/FR-2009-03-11/pdf/E9-5441.pdf).
2010	First clinical trial of human embryonic-derived stem cells for treatment of spinal cord injury [47].
2011	World's first stem cell-derived synthetic windpipe transplant (http://www.newscientist.com/article/dn20671-man-receives-worlds-first-synthetic-windpipe.html#.UzlZGqiSxaY).
2012	Yamanaka wins a Nobel prize for creating induced pluripotent stem cells, which he shares with John Gurdon of the University of Cambridge (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/).
	Blindness eased by historic stem cell treatment [48].
2013	Scientists generate pluripotent stem cells derived from cloned human embryos. Reprogramming human skin cells, using a cloning technique called "somatic cell nuclear transfer" (SCNT) (http://www.nature.com/news/human-stem-cells-created-by-cloning-1.12983).
2014	Charles Vacanti of Harvard Medical School together with Haruko Obokata at the Riken Center for Developmental Biology in Kobe, Japan, and colleagues announced a revolutionary discovery that any cell can potentially be rewound to a pre-embryonic state using a simple, 30-min technique (http://www.newscientist.com/article/mg22129542.500-stem-cell-power-unleashed-after-30-min-dip-in-acid.html#.Uzi-p6iSxaY).
	Masayo Takahashi at the same Riken Center is due to select patients for what promises to be the world's first trial of a therapy based on induced pluripotent stem cells, to treat a form of age-related blindness [49].

Stem Cells and Its Promises

Despite the biomedical research advances of the last 50 years, much is still left to be discovered in human biology and millions of people still suffer from devastating diseases. Stem cell research started in the mid-1800s, and it is viewed from the researcher's point of view that stem cells are the key to understand the biology of various diseases and can lead to treatment and cures, and ultimately saves lives. Stem cells have the ability to literally develop into every cell of the body and thereby have the potential to replace damaged or diseased tissues and to treat disease. Stem cells are considered to have tremendous potential in repairing damaged organs, including the spinal cord, which normally does not undergo regeneration [50–52]. This ability to repair human tissue and to someday provide actual organ systems would provide hope to many with debilitating diseases [53–58].

The most obvious application of human stem cells and the one that receives the most attention are replacement therapies: to replace diseased or degenerating tissues or to replace cell populations, such as those of the hematopoietic system (e.g., blood), that have been destroyed by chemotherapy [59–63]. Stem cells could additionally provide an unlimited supply of specific cell types for transplantation. To date, stem cell-derived cardiomyocyte, neural precursors, and hematopoietic precursors have been transplanted into recipient animals [64–72]. Although the analyses of the long-term outcome of such experiments are limited, the findings suggest that the transplanted cells were able to function in the host animal. Stem cells have a high therapeutic value in the last few years to repair damaged spinal cords [73–76]; cure Crohn's disease and liver cirrhosis [77–84], Alzheimer's, and Parkinson's [85–91]; regrow arteries around a blockage [92–97]; regrow limbs [98–100]; replace failed kidneys and hearts [101–110]; cure diabetes by replacing nonfunctional cells in the pancreas [111–114]; restore vision and hearing [115–123]; and treat leukemia and lymphoma that are nonresponsive to normal therapy [124–129]. These are merely a few of the potential applications of this phenomenal science. In fact most of the treatments listed above have already been studied, and with promising results. However, by latest, miraculous cures that supposedly occurred in faraway lands, the use of stem cells to treat certain degenerative diseases has not advanced beyond mice and needs extensive research.

Other applications of stem cells are in the study of development in both human and animal model systems. This approach includes the identification and isolation of novel precursor cells and of medically important genes. Such genes might encode proteins that have direct therapeutic applications, such as novel growth factors, or genes that would be important targets for drug development [130–135]. Human stem cells will also be valuable as a test system for evaluating the toxicity and efficacy of new medicines or chemicals. The wide ranges of cell types and tissues that may develop from stem cells represent a biological system that mimics many of the complex interactions of the cells and tissues of the body and, as such, provides an attractive and valuable screening tool. This type of assay could have wide applications in the pharmaceutical, chemical, cosmetics, and agrochemical industries. It has the potential to reduce the need for animal testing and to increase efficiency and safety and reduces the costs of developing safe and effective drugs and chemicals [136–140].

Hence, it is clear that stem cell technology continues to revolutionize modern biology and provide unique opportunities in understanding of both the mechanisms that control basic biological processes and in the treatment of diseases. Additional research will be necessary to apply the full therapeutic potential of this technology, but the resulting novel therapies and approaches should more than justify the effort.

Conclusion

Stem cell research provides a useful tool for unraveling the molecular mechanisms that determine the differentiation fate of a pluripotent cell and for understanding the gene expression

properties and epigenetic modifications essential to maintain the pluripotent state. There are many ways in which human stem cells can be used in basic and translational research. However, there are a number of hurdles in the path of stem cell research that are preventing the routine application of the technology in regenerative medicine. This will only be overcome by continuous extensive research. Currently, stem cell research is nearing transplantation therapies with high efficiency whereby a specific cell population compromised by disease is replaced with new, functional cells. The greatest promise of stem cell research may lie in an area not yet imagined.

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