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Translational Stem Cell Research – A Marriage of Hope and Hype

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Abstract

The conventional medicine has failed to treat such disorders which arise by cell dysfunction or death, thus necessitating reimbursement of body's natural regenerative power. Among all the cell types known to date, stem cells provide the best source for augmenting these dysfunctional or dead tissues owing to their intrinsic capability to differentiate into any cell type. Combined with the knowledge of genomics and DNA sequencing, translational stem cell research became not only a reality but it bought a renaissance in regenerative medicine. Like any pioneering technology, this stem cell technology also faced legal, ethical and socio-religious concerns owing to its diverse applications. Human greed and opportunism also crept in which created unnecessary chaos and hype in the sublime and honoured hope which this branch of science had bought into current medicine.

Keywords: Conventional medicine; Genomics; DNA sequencing; Regenerative medicine

Introduction

Today's improved quality of life and an extended lifespan owe much to better healthcare as a direct result of the progress made in science and medicine. The progress was multi-dimensional accompanied with the negative impacts, like pollution of the natural resources, more aged population, hypoactivity, unusual and inappropriate eatables, stress and trauma, etc. These and a host of other factors led to an increase in number of people suffering from such anomalies and disorders for whose cure the existing medical facilities fell short. Most of the disorders were degenerative, the root cause being the dysfunction and death of certain cell types. The most obvious treatment was thus cellular therapy. Despite of reservations from the scientific community, cell therapy progressed considerably in the last two decades and developed into a fourth and final therapeutic pillar for healthcare along with pharmaceuticals, bio-pharmaceuticals and medical devices. This therapy by injection of specific cells into the body paved a hope for treatment of a variety of health problems like diabetes, Alzheimer's, Parkinson's, spinal cord injuries and other neurological disorders, cardiovascular diseases and immune deficiency diseases like AIDS, ALS, etc. This fourth pillar of medicine in itself stood and revolved around stem cells, now known widely as magic cell, cure cells or hope cells, owing to their potential to differentiate into any cell type of the body thereby replenishing the dead cells and curing the disease at the root level. These stem cells act as the utility and repair units of body that serve a central function in maintenance and regeneration of organs and tissues throughout life.

This prized potential of stem cells led to urgent requests from the scientific community and research advocates for research grant, giving ultimately rise to Regenerative medicine – an interdisciplinary approach aiming to repair or replace damaged or diseased human cells or tissues to restore normal function. Thus, regenerative medicine strategies depend upon harnessing, stimulation or tailoring of the endogenous developmental or repair processes. It was therefore, by virtue of its very nature unable to progress without the stem cell research, the knowledge and advancements of which were its guiding torches. Together they hold the promise of revolutionizing the patient care by transplantation of stem cells, progenitor cells or tissue, stimulation of body's own repair processes, use of cells as delivery-vehicles for therapeutic agents as well as in tissue engineering. Deciphering the pathways and mechanisms of differentiation during embryonic and fetal development by genome research was the need of the hour for directing differentiation of the pluripotent embryonic stem cells into any cell type or tissue – the ultimate aim of the regenerative medicine. The information gleaned from the Human Genome Project (HGP) came handy and it could appropriately be said that the confluence of stem cell and genome research marked the renaissance in regenerative medicine.

Discussion

For translational stem cell research, especially involving reprogramming of mature cells into induced pluripotent stem cells (iPSC) and their further differentiation into other cells or tissues, a wide and deep understanding of genomic-wide transcriptional and epigenetic alterations is invaluable. The human pluripoent stem cells (hPSC) are facilitating new types of hypothesis-driven research in human genetics, including studies of complex and multifactorial conditions. When combined with DNA-sequencing technology, a new field of personalized medicine got born. The scalability of cultured PSCs, their stability *in vitro*, potential for genetic modification and capability to differentiate into disease affected tissues makes it possible to study extensively the genotype-phenotype relationships [1]. The combined knowledge of genomics, developmental biology and differentiation pathways makes it possible to generate any cell type from pluripotent stem cell under *in vitro* conditions. Embryonic stem cells have been differentiated across a wide range of cells either spontaneously or upon induction by specific chemicals. Today embryonic stem cells have been developed for almost all the mammalian species. We have been successful in establishing bubaline embryonic stem cell lines from *in vitro* fertilized (IVF), parthenogenetic and cloned embryos [2,3]. We showed differentiation of the cells into wide variety of cells as well as into germ-cell like cells upon spontaneous [4] and induced differentiation under different differentiation conditions [5,6].

The embryonic stem cells are thus capable of both forward (to cells arising from inner cell mass) as well as backward differentiation

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(to gametes). Thus, stem cell research holds enormous potential for understanding of the basic fundamental biology of an organism. Although it is difficult to predict the outcome from basic research, the studies offer the real possibility for treatments and ultimately for cures of many disease for which adequate therapies do not exist, as of now. The first clinical trials and experimental data generated from the use of stem cells have revealed the broad therapeutic potential, in addition to bringing hope to patients suffering from devastating pathologies of different organs and systems. It has not only opened new possibilities in medicine but has kept the stem cells standing at the cutting-edge of modern regenerative medicine and tissue engineering. The first experimental studies aimed at treating degenerative diseases or traumatic injury of central nervous system using fetal or embryonic tissues for isolation of stem or progenitor cells (embryonic stem cells, neural stem cells, spinal precursor cells, etc.). It has been shown that the transplantation of human embryonic stem cells promote functional, behavioral and morphological improvements in experimental animals [7].

It is well understood that for successful treatment of central nervous system disorders, formation of long tracts of axonal outgrowth and synapses at neuromuscular junctions by the grafted cells is a necessity. So far, only a few studies have demonstrated the establishment of functional connections between grafted embryonic stem cells and the host muscle cells after transplantation in animal models of acute injury of the peripheral nerves. It is therefore, presumed that the generation and grafting of support cells for protecting the remaining motonuerons would be more realistic and effective. The successful application of embryonic stem cells for cartilage repair, as a biological pacemaker in cardiac regenerative medicine, peripheral nerve repair, etc. has also been reported by a number of studies. The region-specific stem cells have also been used for repair of the specific tissues and organs. These cells are generated from fetal and adult body tissues (adult stem cells) and have demonstrated higher proliferation, more specific differentiation (multipotent or unipotent), efficient migration after transplantation as well as better regeneration. The human fetal stem cell transplantation has been successfully used in rat model of Parkinson's disease which showed functional integration of grafted fetal dopamine neurons into the host brain and improved motor function in rodent model. Mesenchymal stem cells (MSC), isolated from bone marrow and fat tissue, are multipotent cells which could be used for autologous transplantation, thereby eliminating the risk of graft-versus-host disease. These cells are hypoimmunogenic, interfere with dendritic cell maturation, modulate cytokine production and T-cell responses, inhibit inflammation and the production of extracellular matrix, and secrete soluble factors to create an immunosuppressive environment, thus becoming ideal cells for cellular therapy [8-10].

Adults as well as induced pluripotent stem cells provide excellent sources for autologous cell therapy, in order to completely circumvent the rejection reactions. However, much caution should be taken while using induced pluripotent stem cells, owing to their methods of reprogramming. Embryonic stem cells also prove to be excellent donor cells in reproductive cloning owing to their better reprogramming ability than he adult somatic donor nuclei. The embryonic stem cells, because of their infinite life span and fast self-renewal are extremely useful for development of transgenic cell lines (when transfected with a therapeutic gene) and hence cloned transgenic animals secreting the desired therapeutic protein in body fluids (milk, urine) could be developed.

The use of these cells or their products in cell therapy has gained considerable attention and the approved products for clinical use are under investigation worldwide. The market for such cells and their products is expected to grow enormously, especially in developed countries. The market potential is expected to grow up to 6.6 billion dollars by 2016 from 3.5 billion in 2012 [11].

Conclusion and Recommendations

One of the main shortcomings of the stem cell therapy is that the clinical evidences remain theoretical, based on the assumption that stem cell would differentiate into the appropriate cell type as desired by the clinician. This assumption, however, does not work as the stem cell by its nature could differentiate into any cell type and can even grow into a tumour, thus causing more harm. This adoption of the unproven stem cell therapies by the patients is cutting a big axe at the yet stumbling feet of regenerative medicine. Cell therapies could not be as successfully and surely used as their pharmaceutical counterparts, as they lack batch consistency, stability, safety and efficacy [12]. Thus, the need is to establish cell therapy with proof of concept, understand the exact mechanism of action, the dosage, the kinetics of the therapy and the dynamics of its interaction with other body cells. Lack of this knowledge amplifies the sour notes when it comes to public need, expectation and vulnerability, thereby creating chaos amidst hope. The hope got further hyped and thus downgraded further by the emergence of fraudulent stem cell clinics world over, promoting what is known today as stem cell tourism. These stem cell tourists travel to other countries (mostly from developed countries to developing countries) for hope of getting a panacea to the disease by using stem cell therapy.

The need is to strictly regulate the conduct of translational stem cell research, especially in the developing world where such clinics have mushroomed freely. It thus becomes essential to educate the public and inform it about the ethical and policy issues raised by stem cell research and its applications. However, it must be noted that education alone is not the answer, especially when the tensions emerge between scientists and the public or when the individual is motivated by the very personal desire to improve the life of the loved one or when the boundary between being proactive and being authoritarian gets diffused. The use of unproven stem cell therapy gets further propounded not only due to misinformation and ignorance but also due to lack of any other valuable alternative option. This is part of the complexity of human existence in general and interactions with medically needy but autonomously acting public in particular. Guidelines and policies have been issued at many levels from internal review boards, institutional, state and national ethics committees to National Bioethics Advisory Commission (NBAC) and International Society for Stem Cell Research (ISSCR), The US Food and Drug Administration is actively working in direct-to-consumer marketing of genetic tests and cell products. I believe that community education, engagement between scientists, policy makers and public, appropriate and liberal ethical and legal principles will help to resolve these issues and bring these wonderful inventions and pleasant hopes for the real benefit of future generations. The professionally trained staff having rigorous training in stem cell sciences and related ethics, law and social implications (ELSI) which would objectively explain the risks and benefits of stem cell transplants to the subjects is the need of the day. These stem cell councilors would ultimately help us to develop a bio-psychosocial model of treatment which would attend to the biological, psychological and social dimensions of the illness, integrating objective biomedical data with the patient's subjective experience. Despite of all the hope and hype which have marred stem cell use in regenerative medicine, we still believe in the infinite potential these cells possess for providing the final healing touch to the ailing mankind. Time is not far when we would be able to develop "Universal Donor" cells for transplantation therapies and this fourth pillar of medicine would be used at par and with equivalent safety and precision as its other three counterparts.

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