STEM CELLS IN ORTHOPEDICS: CURRENT CONCEPTS AND POSSIBLE FUTURE APPLICATIONS

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ABSTRACT

Stem cells are the cells that have the ability to divide for indefinite periods in culture and to give rise to specialized cells. Sources of these cells include embryo, umbilical cord and certain sites in adults such as the central nervous system [CNS] and bone marrow. Its use hold promise of wide spread applications particularly in areas of spinal cord injury, difficult non-unions, critical bone defects, spinal fusions, augmentation of ligament reconstructions, cartilage repair and degenerative disc disorders. This review article contains current information derived from Medline searches on the use in various orthopedic subspecialties. Some issues remain at the forefront of the controversy involving stem cell research - legislation, ethics and public opinion, cost and concentration methods. As is true with any new technology, the enthusiasm for this technology that has potential to influence virtually every orthopedic case management, must be balanced by subjecting it to stringent clinical and basic research investigations.

Key words: Stem cells, spinal cord regeneration, non-union, cartilage repair.

INTRODUCTION

A stem cell is a cell that has the ability to divide for indefinite periods - often through out the life of an organism. The stem cells, when provided with the right signals, have the potential to differentiate into different types of cells that constitute an organism. These cells when differentiated can have a characteristic shape and specialized functions, such as heart cells, skin cells or nerve cells. In short, stem cells have two distinctive properties, one they can make identical copies of themselves for a long period of time (self renewal) and two give rise to mature cells that have a characteristic morphology.

Typically stem cell generates an intermediate cell type or different cell types prior to achieving a mature differentiated state. The intermediate cell is called a precursor or

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progenitor cell. Precursor or progenitor cells in fetus or adults are partly differentiated cells and eventually divide and give rise to mature differentiated cell. These cells are often committed meaning that they tend to differentiate only along a particular cellular development pathway; however, some recent studies have shown that this may not be as definitive as was once thought.

Their use in orthopedics has gained a significant momentum in past few years and the field is witnessing some path breaking research currently. This review article contains current information derived from Medline searches on their use in various orthopedic subspecialties.

Sources of stem cell
Stem cells are derived from three main sources: embryos, adults and the umbilical cord.

Embryonic stem cells: These stem cells are defined by their origin, which is from one of the earliest stages of development of the embryo called blastocyst. More specifically these are derived from the inner cell mass of the blastocyst at a stage before it would implant in the uterine wall. These cells can self replicate and are pluripotent.[8-16]

Adult stem cell: It is an undifferentiated cell that is found in a differentiated tissue, it can renew itself and become specialized to yield all the specialized cell types of the tissue from which it originated. Sources of adult stem cell have been found in the bone marrow, blood stream, cornea and retina of the eyes, the dentine, liver, skin, pancreas and gastro intestinal tract. In contrast to the embryonic stem cells, these are not capable of forming all the cells of the body that is they are not pluripotent. Adult stem cells are rare and their primary function is to maintain homeostasis and to a certain extent repair and replace the cells that die because of injury or disease. Adult stem cells are dispersed throughout a mature animal and behave very differently depending on the local milieu. Another feature that distinguishes the adult stem cell from the embryonic stem cell is the fact that adult stem cells share no common features and thus have no means of characterization; as opposed to these the embryonic stem cells can be defined by their origin that is the inner cell mass of blastocyst. The origin of the adult stem cells remains a controversy till date. The most accepted hypothesis suggests that the stem cells are somehow set-aside during the fetal development and restrained from differentiating.[8-16]

Umbilical cord stem cells: These are cells harvested from the cord blood. Cord blood is rich in the stem cells and after appropriate human leukocyte antigen [HLA] matching may be used to treat a variety of conditions. Characteristics of these cells are identical to adult stem cells except that they are not derived from adults and that their concentration is far more in umbilical blood as compared to adults. The use of umbilical cord stem cells in orthopedics is still in a nascent stage and most studies currently focus on the use of the adult stem cell.[17-18]

ORTHOPEDIC APPLICATIONS

Spinal Cord Regeneration
Injury to neural tissue results in a permanent deficit as neurons do not have the ability to repair or regenerate. Isolation and preparation of specific population of adult stem cells have evolved to the point of a stable, long term culturing with capacity to differentiate into neural phenotypes from all three neural lineages: neurons, astrocytes and oligodendrocytes. In animal experiments different varieties of adult stem cells viz - olfactory ensheathing cells, cultured spinal cord stem cells and dermis-derived stem cell have been implanted in a rat model of spinal cord injury. And although no definite conclusions were reached on which of them is best for neural injuries, each of these showed ability to incorporate into spinal cord, differentiate and improve the locomotor capability.[27] The presence of neural stem cells [NSC] in the adult mammalian spinal cord suggests the latent capacity of regeneration of injured spinal cord if the NSC are activated properly. In this situation it is crucial to understand the underlying mechanisms of maintenance, activation and differentiation of neural stem cells and subsequent process, including the migration, survival and functional maturation of differentiated cells which may be possible by further studies.[28,29] Experiments involving the use of human umbilical cord blood, a rich source of non-embryonic stem cells, showed that cord blood derived stem cells migrate and participate in the healing of neurological defects caused by traumatic assault. Human experiments involving paraplegic people is still a distant future in most nations of the world; however, certain reports that have originated from main land China and Portugal have concurred with results of animals experiments in terms of improvement in neurological recovery following stem cell infusions.[30]

Critical Bone Defects and Non-unions
Critical defect is defined as a loss of a portion of bone that fails to heal and requires a bone reconstruction to prevent a non-union defect. The ideal modality for management of these defects have so far been the autologous bone grafting procedures, but since the amount of the autologous bone graft that can be harvested remains limited and also conditions like osteoporosis precludes its use, alternatives are aggressively being explored. Some investigators have directed their attention towards the use of autologous non hematopoetic /progenitor cell contained in the adult bone marrow stroma (also referred to as adult stromal cell). Two methods have been employed in the pre-clinical and clinical protocols while managing the critical defects. In one of the protocols the stem cells were directly injected at the lesion site and in other they were expanded ex vivo before being implanted. The authors concluded that both the approaches were equally correct in principle but will require further studies to demonstrate unambiguously their efficacy in such conditions.[31,32]

Cartilage Repair
Most authors agree that biologic solutions in treating cartilage injuries and degeneration would be preferable over the joint arthroplasties. Recently the researchers are reviewing the use of periosteal derived stem
cells in the repair of osteochondral defects for a variety of reasons. Primarily the cells can be easily expanded in culture and are phenotypically stable as well as they are ideal for the delivery of various genes promoting the repair, maintenance and anabolic metabolism of the cartilage injuries. Adult stem cells appear to be an attractive option as progenitor cells for cartilage due to their documented osteogenic and chondrogenic potential. The differentiation of mesenchymal stem cells [MSC] along chondrogenic lineage may be a possibility in near future by a multi disciplinary approach involving the molecular medicine, biomedical engineering, polymer chemistry, cell biology and clinical orthopedics to get an insight in regulatory mechanisms controlling the lineage transitions and maturation of cartilaginous tissue.

ACL Reconstruction Augmentation

In a preclinical study conducted on 48 rabbits for ACL reconstructions coated with stem cells, it was proved that incorporation of stem cells resulted in healing by formation of the intervening zone of cartilage resembling the chondral enthesis of normal ACL insertions rather than collagen fibers and scar tissue. Biomechanically, ACL reconstructions enhanced with stem cells had better strength and stiffness. Stem cells have the potential to provide stronger ligament reconstructions physiologically and biomechanically in the near future. Meniscal tears in the avascular zone have limited capacity to heal due to inadequate blood supply. In a pre-clinical study conducted on Sprague-Dawley rats by transplanting mesenchymal stem cells into meniscal defects it was observed that MSC could survive and proliferate in the meniscal defects. MSC transplantation appears o promising new strategy for treatment of meniscal tears in avascular zone.

Muscular Dystrophies

Muscular dystrophies are group of disorders, which are associated with serious clinical implications, but there is still no cure. Myoblast transfer therapy has long been viewed as a potential therapy for Duchenne's muscular dystrophy which entails transplantation of committed mouse precursor cells into the muscle cells but has had limited success in clinical trials. The recent discovery of the population of cells within adult muscle with stem cell like characteristics may have great impact in future advances in transplantation therapies for muscular dystrophies.

Spine Fusion

In a study conducted on a murine model, spine fusion was achieved by injecting genetically engineered MSC into the paravertebral muscles. It was observed that spine fusion can be achieved by engineered mesenchymal stem cells that conditionally express bone morphogenetic protein-2 and the extent and quantity of the newly formed bone can be monitored by controlling the duration of rhBMP-2 gene expression. Use of marrow derived stem cell along with allograft to achieve spinal fusion has been supported by many authors when significant quantity of osteogenic tissue is required. Secondly it has been hypothesized that mesenchymal stem cells are deficient at fusion site in certain situations [e.g. smokers, posterolateral fusion beds, cases of failed fusions]. In such scenarios introduction of stem cells can aid in bone healing and also shorten the duration of spine fusion.

Intervertebral Disc Degeneration

Intervertebral disc degeneration is manifested by gradual loss of water and proteoglycans within the intervertebral disc, which may be due to inability of the ageing disc cells to maintain their structural integrity. Recently mesenchymal stem cells have been found to have the potential to differentiate into nucleus pulposis like cells capable of synthesizing proteoglycans rich extracellular matrix characteristic of healthy intervertebral disc when exposed to appropriate microenvironment (hypoxia, three dimensional culture). Although the problems pertaining to proliferation of stem cells within degenerative disc need to be overcome, the potential for MSC therapy to retard or reverse degenerative process appears significant.

Challenges and the Road Ahead

Some issues remain at the forefront of the controversy involving stem cell research - legislation, ethics and public opinion, cost and concentration methods. Legislations regarding the use of stem cells vary among different countries as does the public opinion and the moral high grounds assumed by various political and religious groups. Researchers argue that many of the embryos created by in vitro fertilization programs are surplus to requirements and are in any case normally destroyed. These can be potentially used for the derivation of ES cells. Costs involved in stem cell research is astronomical and thus is limited to centers that can invest huge sums of money for various projects. This cost is eventually passed on to patients and the health care system. With time however it is expected that cost would bottom down and the technology may be affordable to most candidates.

One of the challenges that clinicians face while using the adult stem cell is that of concentrating the cells. The normal concentration of stem cells in samples drawn from marrow is many a times considered inadequate for use in most scenarios. Various techniques like filtration, culture expansion and sieving are employed for this purpose.

Success of stem cells pertaining to various modalities has been limited by problems of dosage, lack of activity of the recombinant factor and the inability to sustain the presence of a factor for an appropriate length of time. Also the risk of forming unwanted tissues and teratocarcinomas by the stem cells require further evaluation and long term follow ups.

CONCLUSION

The use of stem cell in orthopaedics has provided a new arena for managing complex conditions. Its use holds promise of wide spread applications particularly in areas of spinal cord injury, difficult non- unions, cartilage repair and degenerative disc disorders.

However, its use at present time is...
restricted by lacunas in our knowledge in differentiating potentials of these cells and concerns over the long term stability of repair tissue derived from these cells. In view of concerns raised by certain politico-religious groups and also as with any new technology, the enthusiasm for this technology that has potential to influence virtually every orthopedic case management must be balanced by subjecting it to stringent clinical and basic research investigations.

REFERENCES

New international Child Growth Standards for infants and young children released by the World Health Organization (WHO) provide evidence and guidance for the first time about how every child in the world should grow. The new WHO Child Growth Standards confirm that children born anywhere in the world and given the optimum start in life have the potential to develop to within the same range of height and weight. Naturally there are individual differences among children, but across large populations, regionally and globally, the average growth is remarkably similar. For example, children from India, Norway and Brazil all show similar growth patterns when provided healthy growth conditions in early life. The new standards prove that differences in children's growth to age five are more influenced by nutrition, feeding practices, environment, and healthcare than genetics or ethnicity. With these new standards, parents, doctors, policymakers and child advocates will know when the nutrition and healthcare needs of children are not being met. Under-nutrition, overweight and obesity, and other growth-related conditions can then be detected and addressed at an early stage.

"The WHO Child Growth Standards provide new means to support every child to get the best chance to develop in the most important formative years," said Dr. Lee Jong-wook, Director-General of WHO. "In this regard, this tool will serve to reduce death and disease in infants and young children."

The new Standards are the result of an intensive study initiated by WHO in 1997 to develop a new international standard for assessing the physical growth, nutritional status and motor development in all children from birth to age five. WHO and its principal partner, the United Nations University, undertook the Multicentre Growth Reference Study (MGRS) which is a community-based, multi-country project involving more than eight thousand children from Brazil, Ghana, India, Norway, Oman, and the United States of America. The children in the study were selected based on an optimal environment for proper growth: recommended infant and young child feeding practices, good healthcare, mothers who did not smoke, and other factors associated with good health outcomes.

Since the late 1970s, the National Center for Health Statistics / WHO growth reference has been in use to chart children's growth. This reference was based on data from a limited sample of children from the United States. It contains a number of technical and biological drawbacks that make it less adequate to monitor the rapid and changing rate of early growth.