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BASICS OF STEM CELLS THERAPY

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ABSTRACT
Regeneration of a lost tissue is known to be great challenge for several years, in the recent past the research on regenerative medicine has gained great importance and scientific advancements in the field of molecular biology. Understanding the biological concepts in the tissue regeneration coupled with experiments on stem cells is likely to result in a great shift in the therapeutic medicine. Stem cells have been successfully isolated from variety of human tissues. Initial evidence from pioneering studies has documented that stem cells play vital role in treatment for various life-threatening diseases that have so far defeated modern medical care. The recent studies have been exploring the role of stem cells and their applications. This review discusses in brief the origin of stem cells, their properties, characteristics. It also focuses on current research, their potential applications and the various challenges and barriers that we must overcome before translating laboratory results to successful clinical applications.

Keywords: stem cells; stem cell therapy; successful clinical applications

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INTRODUCTION

Stem cells have the unique ability to self-renew or differentiate into various cell types in response to appropriate signals. These properties provide stem cells with unique capabilities for tissue repair, replacement and regeneration, making them valuable therapeutic purposes and research tools in regenerative medicine and stem cell therapies. They can differentiate into specific cell types under the right conditions (Yolanda et al., 2014). Since stem cells have the ability to turn into various other types of cells, scientists believe that they can be useful for treating and understanding diseases. They can be used to grow new cells in a laboratory to replace damaged tissues, correct parts of organs that don't work properly, research causes of genetic defects and how diseases occur, moreover can be used to test new drugs for safety and effectiveness (Squillaro et al., 2016).

Stem cells occupy an active and growing area of basic science and clinical research due to their ability to self-renew and differentiate into mature cell types. Current clinical applications for stem cells include treatment for neurological and cardiovascular diseases, autoimmune disorders, cancer, wound healing and drug screening. Newly discovered gene editing technologies like CRISPR may advance stem cell research and offer enormous promise in treating difficult disorders. Stem cells are broadly characterized into multipotent and pluripotent stem cells (Yolanda et al., 2014 & Jacquelyn, 2017).

Multipotent stem cells include adult stem cells that can self-renew and differentiate into specialized, tissue-specific cell types such as hematopoietic stem cells (HSCs) that differentiate into various blood cells making new red blood cells, white blood cells, and other types of blood cells. So it can be used for bone marrow transplants and treatment of certain types of cancer (Jacquelyn, 2017). Mesenchymal stem cells (MSCs) are other type of multipotent non-hematopoietic stromal cells that differentiate into osteoblasts, myocytes, chondrocytes, adipocytes and neural stem cells (NSCs) that differentiate into neurons, astrocytes and oligodendrocytes. Furthermore, MSCs can cross their lineage and differentiate into other cell types such as hepatocytes, keratinocytes, and neurons (Zappia et al., 2005).

The mesenchymal cells (MSCs) have the ability to regenerate damaged tissue via paracrine molecules that allow cell to cell cross talk and thus balance out the inflammatory process and help the progenitor cells inside the tissue to develop and transform. These molecules include growth factors, morphogens, and chemokines. The ability of these cells allows them to reduce inflammatory reactions and fibrosis whilst enhancing the development of blood vessels and new tissue formation (Boulos et al., 2021). It is accepted that MSCs function in a paracrine manner in vivo and not by direct differentiation. In addition to soluble factors, exosomes are now supposed to be important mediators for the paracrine effect of MSCs and possess similar functions to MSCs (Yu et al., 2016).

Pluripotent stem cells can differentiate into any cell lineage. They are classified based on the tissue of origin into embryonic stem cells (ESCs), perinatal stem cells, and induced pluripotent stem cells (iPSCs). ESCs are derived from embryos three to five days old and can divide indefinitely in an *in vivo* stem cell culture. Perinatal stem cells are derived from umbilical or placental blood or tissue and are the most widely used pluripotent stem cells. Cord blood banking at birth is increasingly accepted as an option for treating complicated disorders later in life. The iPSCs are adult cells that are reprogrammed to behave like ESCs. The advantage of using iPSCs for medical applications is the reduced chance of graft rejection, since the cells are derived from the patient's own tissues (Jeon et al., 2016).

The main challenges of cell replacement therapy include the delivery and integration of regenerative materials to the eye, overcoming the opportunity of immune rejection and the guidance of neural growth to establish functional connections (Gater et al., 2016). Stem cells require specialized, high-quality media and expert culture techniques for propagation in the laboratory. Suboptimal stem cell culture conditions can easily lead to unwanted stem cell differentiation (Jacquelyn, 2017). Stem cells that are cultured and transported in the right medium to the laboratory is centrifuged, trypsinized, and propagated under ideal conditions and stored in the master cell bank (MCB). MCB is further passaged to yield colonies of stem cells, given the right inductive signals using appropriate growth factors to allow them to differentiate into required cell types. These are injected or implanted into a patient as cell-based therapy. Homing will ensure that the stem cells reach the target tissues. Stem cells can be delivered by two ways; intravenous injection (direct delivery of cells) and cell encapsulation systems (indirect delivery of cells using a carrier). The cell encapsulation approach uses a biocompatible, biodegradable material construct that is seeded with cells and implanted into defects to regenerate the lost tissue (Fuchs et al., 2005).

MSCs could be isolated from many tissues. Nowadays, much focus has been given to adipose tissue as an accessible and a rich source of MSCs. Comparatively, adipose-derived mesenchymal stem cells (AD-MSCs) possess more superior characteristics than bone marrow-derived mesenchymal stem cells (BMMSCs) and considered recently by researchers

as the ultimate source for the adult stem cells (Luna et al., 2014). AD-MSCs can be easily isolated in higher amounts with less discomfort to the donor. Additionally, AD-MSCs are known to undergo senescence later than BM-MSCs and have a higher proliferative capacity. In addition, AD-MSCs inhibit the proliferation and cytokine secretion of T cells in response to mitogens. Furthermore, AD-MSCs produce immune modulators and some growth factors such as vascular endothelial growth factor and insulin -like growth factor more than BM-MSCs (Mohamed et al., 2018 & Barakat et. Al., 2020).

A study was conducted to evaluate the potential therapeutic role of AD-MSCs in enhancing the myelination process of the demyelinated white matter of the central nervous system in a cuprizone-induced experimental model of multiple sclerosis on rats. This study stated that intravenous administration of AD-MSCs in Cuprizone treated group enhanced the remyelination process, improved the motor and cognitive functions and decreased the oxidant level. The study concluded that AD-MSCs provide a valuable potential treatment for neurodegenerative demyelinating diseases such as MS (Barakat et. Al., 2020). In addition, another study was conducted to evaluate the beneficial outcomes of rebamipide and microvesicles come from mesenchymal stem cells on treatment of acetic acid induced experimental model of ulcerative colitis on rats , which proved that both rebamipide and microvesicle improved the prompted ulcerative colitis, but their combination was more effective (Helal et al., 2019).

BMMSCs secrete microvesicles (MVs) that play a significant role in repair and differentiation of impaired tissue. MVs carry the same character of the cells from which they isolated, they are composed of membrane fragments surrounding bioactive lipids, cytoplasmic proteins and nucleic acids, moreover they act as key communicators among cells to transport proteins, lipids and nucleic acids. Paracrine signals such as Coding and noncoding RNAs are also passed in such microvesicles. So, these vesicles afford a new supplier and a great potential donor for regenerative medicine, reestablishing normal structure and function of injured tissue through their capability to deliver molecules improving cell division (Sayed et al., 2017 & Kourembanas, 2015). Furthermore, a study was conducted to evaluate the possible potential therapeutic effect of bone marrow derived Mesenchymal stem cells (BMMSCs) and their exosomes (BMMSCs-exosomes) on induced diabetic retinopathy in rats and concluded that MSCs and exosomes can treat diabetic retinopathy. However, better results can be obtained when exosomes were given with MSCs (Abd El-Halim et. Al., 2020).

Exosomes are extracellular vesicles generated by fusion of multivesicular bodies (MVBs) with plasma membrane. They are released by several types of cells, including mast cells, dendritic cells, B lymphocytes, neurons, adipocytes, endothelial cells, epithelial cells and mesenchymal cells. Exosomes have recently come into focus of research based on their high capacity to interact with target cells and their ability to selectively modify cell signaling (Rashed et al, 2017 & Beer et al., 2017 and Yin et al., 2019). Another work was designed in a trial to establish an optimum protocol for in vitro cardiomyocyte differentiation using azacytidine starting from bone marrow-derived mesenchymal stem cells (BM-MSCs). It was concluded that use of 5-aza showed a valuable differentiating effect on MSCs towards cardiomyocytes. Prolonged use of the differentiating medium resulted in promotion of the differentiation. Yet, it was at the expense of the viability of these cells (El Sawy et al., 2020).

Azacytidine (Aza; 5-Aza), a DNA demethylation agent, is an analogue of cytidine. The US Food and Drug Administration approved the drug for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukemia, and acute myeloid leukemia. Moreover, many

studies have shown that 5- aza can induce stem cells to differentiate into cardiomyocytes, but some issues regarding its cytotoxicity are still unknown. Recently, stem cell-based myocardial regenerative therapy has become a promising alternative for dealing with ischemic myocardial diseases. Mesenchymal stem cells (MSCs) are particularly suitable for cell replacement therapy as they are multipotent, low immunogenic, easily isolated and purified with high expansion potential (Mathiasen et al., 2015 & Wehmeyer et al., 2018).

Comparison was done between effect of Microvesicles (MVs) versus Mesenchymal stem in induction of differentiation, this study compared two new approaches in treating glucocorticoids induced osteoporosis in temporomandibular joints (TMJs) of albino rats, Microvesicles (MVs) and Mesenchymal stem cells (MSCs) and concluded that microvesicles treated TMJs showed an enhanced pattern of bone regeneration confirmed by the higher mean bone area % as compared to MSCs group. On the contrary, MSCs treated TMJs showed a significantly elevated level of osteogenic markers; yet the osteogenic reactivity was very aggressive that caused deformity to the TMJ architecture. A key point in the previous study was that the local injection of microvesicles improved the histopathological and biological changes associated with osteoporosis in the treated side and in the opposite side that didn't receive MVs. This could be referred to the rapid action of MVs; as MVs are formed of genetic material, ready to induce its action and easily to transfer from one site to another. On the other hand, the effect of MSCs was markedly localized. This was confirmed by the marked improvement in all the osteogenic markers in the treated side as compared to the untreated side but unfortunately caused a deformity in the TMJ with shrinkage in its size due to excessive bone formation on the expense of the marrow spaces (Abdel Moneim et. al., 2020).

Because of the overwhelming success of animal studies, numerous clinical trials are now going on world over. Various therapeutic programs are exploring the role of stem cells and their microvesicles and exosomes therapy for many conditions like Parkinson's disease, spinal cord injury, heart failure, hematological disease, cancer, arthritis, diabetes, and peripheral vascular disease. Preliminary results from the pilot studies are encouraging and have led the US FDA to permit Phase III clinical trials for acute and steroid refractory graft versus host disease and Crohn's disease, Phase II clinical trials for the repair of heart tissue following a heart attack, the protection of pancreatic islet cells in patients with type 1 diabetes, and the repair of lung tissue in patients with chronic obstructive pulmonary disease (Daley and Scadden, 2008 & Tateishi et al., 2008).

Conclusion

Stem cell therapies have virtually unlimited medical applications. While there are several barriers that need to be broken down before this novel therapy can be translated from lab to clinics. We need high-quality research coupled with collaboration between basic scientists and the clinicians. A team effort engaging the expertise of the molecular biologists, immunologists, biomaterial scientists, cell biologists is crucial in reaching the desired goal. Stem cell therapy has brought in a lot of optimistic hope among researchers, doctors, and patients who are the chief beneficiary of this innovation.

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