Stem Cell Therapy in Esophageal Disorders

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ARTICLE INFO
Keywords:
Stem cells
Esophagus
Inflammation
Stricture
Dysphagia

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ABSTRACT
Disorders of the esophagus could include various conditions such as inflammation, stricture or esophageal-phase dysphagia. Management of these disorders is rapidly developing, which includes conservative, surgical and modern techniques such as the use of stem cells. Stem cells are characterized as cells which have not differentiated, able to multiply and differentiate into multiple organ cells, and has the ability of self-renewal which is vital in disease management. Mesenchymal stem cells or MSCs are mature stem cells with multidirectional differentiation and also have the ability of self-renewal. It includes adipose MSCs (AMSCs), bone marrow MSCs (BMSCs), umbilical cord MSCs (UC-MSCs) and gingival MSCs. Based on the characteristics of stem cells as well as the anatomy and physiology of the esophagus, stem cells may have a role in the management of esophageal disorders.

1. Introduction

Stem cells are human cells which have not specialized in any specific function, characterized as cells that have not yet differentiated, able to multiply and differentiate into multiple organ cells, and has the ability of self-renewal. Stem cells are present in embryonic and mature cells, in which its differential potential is dependent on its type and characteristics. Stem cells may differentiate to specific cell types in vivo, which may have totipotent, pluripotent, multipotent or unipotent properties.¹,²

Embryonic stem cells in the morula phase are totipotent cells which have the differentiation potential to shape a complete individual being. Its potential may decrease along the embryo development from totipotent to pluripotent.³ Mature stem cells are cells that do not differentiate their selves within the tissue, and are capable of differentiation and self-renewal as well as specializing to form the needed tissue. Mature stem cells may be either pluripotent or unipotent.⁴ The most prominent pluripotent stem cells are hematopoietic stem cells; that can differentiate at least into 12 types cell blood; and mesenchymal stem cells (MSCs) that have multidirectional differentiation and the capability for self-renewal. Mesenchymal stem cells that often used for therapy are adipose MSCs (AMSCs), bone marrow MSCs (BMSCs), umbilical cord MSCs (UC-MSCs) and gingival MSCs.⁵,⁶

A comprehensive understanding regarding the characteristics of stem cells and its role in regenerative treatment, tissue engineering and gene therapy, may support the management of several diseases such as cardiovascular, neurological, bone and cartilage and inflammation diseases. Management of esophageal disorders which incorporates stem cells is still scarce, though it is thought that the mechanism of stem cells in esophageal disorders are similar to stem cell therapy in other diseases.⁵

2. Stem Cells

Stem cells are undifferentiated cells that are capable of self-renewal, differentiation and remodeling of host tissues in vivo.⁴ Stem cells do not yet have a specific shape and function, and are characterized as undifferentiated, able to
reproduce, and able to differentiate into more than one type of cell. According to their development, stem cells are divided into two types, namely embryonic stem cells and mature stem cells. Embryonic stem cells are found when the individual is still in the embryonic stage, which is an inner cell mass found in the blastocyst phase, has long telomeres and high telomerase enzyme activity and has high cell proliferation power. Mature stem cells are a group of undifferentiated cells found in an inactive state in a tissue that has had a specific function in the individual’s body. The existence of these stem cells is thought to maintain homeostasis in the tissues where they are located.  

The potential of stem cells is tiered, ranging from stem cells that are totipotent to unipotent. Totipotent stem cells have the highest differentiation ability and allow cells to form embryonic and extra-embryonic structures, such as zygotes. The next characteristic of stem cells is pluripotent or pluripotent stem cells (PSCs), which can form almost all types of cell organisms including germ cells, but cannot form placental tissue. This trait is shared by embryonic cells and germ cells. The next characteristic of stem cells is multipotent, in which these cells have a narrower differentiation spectrum than PSCs but can develop specifically in discrete cells of certain cell lineages. Mature stem cells are multipotent, for example, hematopoietic stem cells that can develop into several types of blood cells. These hematopoietic stem cells after re-differentiating, will be oligopotent where the ability to differentiate is only limited to cells from their lineage. Myeloid stem cells are an example of oligopotent stem cells that can develop into white blood cells but cannot become red blood cells. The last characteristic of stem cells is unipotent, where the ability to differentiate is the narrowest and the special trait is to divide repeatedly. This latter property makes these stem cells a promising candidate in regenerative medicine because these cells can only form one type of cell, for example muscle stem cells and neurons. The classification of stem cell potential into 5 types above is inconsistent, in which recent research has shown that the difference between pluripotent and multipotent is becoming unclear, and some cells have a greater potential than previously thought. Stem cells in the body are in a state of inactivity for long periods of time until they receive the appropriate signal to start and eventually stop dividing. Strict control of the in vivo self-renewal process is needed to ensure stem cells do not divide uncontrollably which will lead to overgrowth such as cancer. Signals that affect stem cell activity can be divided into external signals, such as physical contact between cells or chemical secretion by surrounding tissues, and internal signals, which are signals controlled by genes in DNA.

There are many advantages of stem cell therapy, but there are still significant safety considerations due to the tumorigenicity of embryonic stem cells. Alternatively, mature stem cells that can be found in almost all tissues including brain, dental pulp, muscle, bone marrow, skin and pancreas have been extensively characterized for their therapeutic potential. Mature stem cells are multipotent cells, such as hematopoietic stem cells (HSCs) which produce all blood cells and mesenchymal stem cells, and mesenchymal stem cells (MSCs) which produce bone, fat, cartilage and muscle or unipotent mature stem cells such as progenitor cells.  

Mesenchymal stem cells (MSCs) have self-renewal properties and are able to differentiate into osteogenic cells, chondrogenic cells, adipose cells and various other cells. MSCs have low immunogenicity and strong immunomodulating potential, can be identified and isolated from various tissues such as bone marrow, adipose tissue, skin tissue, intervertebral disc, amniotic fluid, various types of dental tissue, human placenta and umbilical cord blood. MSCs function is to maintain tissue homeostasis, and they have great potential in regenerative therapy. These cells have been successfully used in clinical therapies such as bone and cartilage repair, skin wound healing, neuronal regeneration, heart tissue regeneration and the treatment of immunologic disorders. This is due to the ability of these MSCs in homing, multilineage differentiation and immunomodulation.

3. Stem Cell Therapy in Esophageal Disorders

Stem cells have many characteristics and can be used to treat various diseases. Currently, the use of stem cells for the treatment of esophageal disorders is still developing but it is still not a widely used treatment. Several literatures have studied stem cell therapy for esophageal disorders, such as ulceration due to gastric acid reflux, corrosive esophagitis, esophageal stricture, radiation-induced esophageal injury, esophageal reconstruction, and stem cell therapy for dysphagia. The esophagus originates from the anterior endodermal foregut which also forms the respiratory system. In the process of development, the lining of the esophagus shifts from a simple columnar epithelium to a layer of stratified squamous cells accompanied by the replacement of the unspecified mesenchyme with a layer of muscle cells. Recent studies using various animal models have shown that a number of signaling pathways and transcription factors play an important role in the process of epithelial morphogenesis and the role of human pluripotent stem cells in the management and assessment of the pathophysiological process of disorders of the esophagus.

The most common esophageal disorder is esophageal ulceration. Esophageal ulceration is caused by reflux of gastric acid resulting in
necrosis of the superficial layers of the esophageal mucosa, followed by erosion and ulceration of the esophagus. The prevalence of esophageal ulceration due to gastrointestinal reflux is about two to seven percent.\textsuperscript{10} The ulcer healing process includes inflammation repair, cell migration and epithelial regeneration, neovascularization, gland and matrix regeneration, thus alternative cells such as stem cells are needed to fill the gaps and reconstruct these ulcerated tissues. Adipose-derived stem cells (AD-MSCs) are mesenchymal stem cells of choice for repair of these ulcers because they release VEGF, TGF-β, FGF and HGF growth factors, improve vasculogenesis and inhibit the inflammatory process.\textsuperscript{11}

In several head and neck tumor patients undergoing chemoradiation, the esophageal mucosa will experience inflammation in the form of edema and hyperemia which can lead to several complications such as pain, dysphagia and burning sensation in the retrosternal region. This condition can lead to decreased food intake, malnutrition, dehydration and electrolyte disturbances as well as pain. These complications result in impaired quality of life in patients requiring supportive and symptomatic therapy, thus supporting the exploration of stem cell therapy as treatment of radiation-induced esophageal mucosal damage. A recent study on the effectiveness of dental pulp stem cells (DPSCs) in rats subjected to radiation showed that the esophageal lumen of experimental animals that were irradiated would experience congestion, edema, effusion of inflammatory cells, exfoliation and release of inflammatory cytokines such as TNF-α, IL-1β, and IL-8 as well as necrosis of the esophageal mucosal epithelium, resembling the clinical features of radiation-induced acute esophagitis. The use of transplantation of dental pulp stem cells (DPSCs) in this case has the advantage because DPSCs, which are a type of mesenchymal cell, have high proliferative ability and are able to differentiate into various types of cells, including epithelial cells. This study showed an improvement of the esophageal mucosa which was characterized by a significant increase in cell surface markers such as CD71, CK14, integrin 6, and PCNA as well as decreased levels of inflammatory cytokines. This study shows that DPSCs can be an alternative source of stem cells for tissue regeneration and could be a potential therapy for the treatment of radiation-induced injury.\textsuperscript{12}

Esophageal disorders can also be caused by trauma due to corrosive chemicals, both acids and bases. The mucosal layer will be damaged when exposed to corrosive substances. The healing process in exposure to corrosive substances can cause complications in the form of fibrosis and stricture, and in severe cases perforation can occur. Among the currently available therapies, a standard therapy for this condition has not been established. Kantarcioglu, et al in 2014 used 65 Wistar rats to assess the effectiveness of bone marrow MSCs taken from the tibia and femur bones of the mice and cultured in vitro to be injected into experimental mice that had been exposed to corrosive substances in their esophagus through the tail vein of the mice.\textsuperscript{13} Histopathological examination, determination of submucosal collagen, mucosal muscle injury, intrinsic muscle injury and collagen deposition, calculation of esophageal stenosis index and positron emission tomography were performed to evaluate the results of this study. The results of this study showed that the structure of the esophageal epithelium was not completely regenerated, but that these bone marrow MSCs showed positive homing and differentiation features in the esophageal epithelium of mice.\textsuperscript{5,13}

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection are the most common operative procedures for esophageal malignancies. Both of these procedures have complications in the form of stricture formation in the esophagus, so efforts to prevent the formation of these strictures are vital. Oral and intravenous steroids are widely used to prevent the formation of these strictures, but with unsatisfactory results. A research conducted by Perrod, et al in 2016 used adipose-derived stromal cells (ADSCs) to prevent stricture formation after operative endoscopic procedures on the esophagus using pigs as experimental animals.\textsuperscript{12} Adipose-derived stromal cells are known to have the ability to modulate keratinocyte-fibroblast interactions so as to improve the quality of regenerated tissue by suppressing excessive fibrosis development. Adipose-derived stromal cells also have anti-inflammatory properties, able to modulate the local immune system, and induce neovascularization. Adipose-derived stromal cells are formed in a tissue engineering construct and arranged in two layers of cell sheets. These two layers of cell sheets are then placed using a paper support membrane right at the surgery site immediately after the operative endoscopic procedure. Adipose-derived stromal cells influence the inflammatory response process by producing TGFβ, PDGF and IL-13. TGFβ1 stimulates fibroblasts to become myofibroblasts which will improve the wound healing process. This study showed that transplantation of ADSCs reduced the incidence of stricture formation after surgery.\textsuperscript{14}

Swallowing function is strongly influenced by the superior laryngeal nerve. Lesions that affect this nerve, either due to trauma or surgical procedures such as neck dissection and thyroidectomy, can interfere with swallowing function. Therefore, it is important to determine effective therapy in patients with dysphagia due
to lesions of the superior laryngeal nerve. Stem cell-based research is a promising technique in the regeneration of neural tissue using stem cells from human exfoliated deciduous teeth (SHEDs) and human dental pulp stem cells (hDPSCs). This study used rats to assess the effectiveness of human exfoliated deciduous teeth (SHEDs) therapy against superior laryngeal nerve lesions. From the results of this study, it was found that the swallowing function of the experimental animals had improved in the swallowing process and the function of the superior laryngeal nerve. From histological examination, it was found that SHEDs were effective in regenerating nerve cells, in this case the lesion of the superior laryngeal nerve.15

It is to be noted that the usage of stem cells in dysphagia management is still not yet extensively studied, and this may be due to difficulties in isolating the targeted intervention, considering the number of conditions that may cause esophageal disorders. In esophageal dysphagia such as dysmotility congenital, achalasia, or even refractory GERD treatment, stem cell therapy may have a role in their management. Lack of data and the substantial decrease in quality of life of patients suffering from esophageal motility disorders may lead to further studies.8

4. Conclusion

Stem cells are capable of multilineage differentiation and self-renewal. Stem cells may differentiate into several cell types in vivo and can be categorized as totipotent, pluripotent, multipotent, and unipotent stem cells based on their differentiation potential. Mesenchymal stem cells (MSCs) are most commonly used due to its low difficulty in isolation and culture thus enabling numerous studies regarding MSCs. MSCs are mainly from the adult bone marrow, umbilical cord, placental blood and adipose tissue. Adipose tissue is commonly used in studies of stem cells. Isolated mesenchymal stem cells could be used for managing damaged tissues and organs as well as functional failure; it has low immunogenicity and can reduce exclusion effects during cell transplantation.

The role of stem cells in the management of esophageal disorders are still not fully understood. Studies and clinical trials of stem cell therapy in esophageal disorders are still lacking, though theoretically it may show great benefits for the patient’s quality of life and may lead to further scientific advancement.

5. Acknowledgements

None

6. References


