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Editorial Board Member of *World Journal of Stem Cells*, Irfan Khan, PhD, Assistant Professor, Stem Cells Lab. P-132, Dr. Panjwani Center for Molecular Medicine and Drug Research, University of Karachi, Karachi 75270, Pakistan

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Strategies for treating oesophageal diseases with stem cells

Yang Gao, Shi-Zhu Jin

ORCID number: Yang Gao (0000-0002-7040-5260); Shi-Zhu Jin (0000-0003-3613-0926).

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Yang Gao, Shi-Zhu Jin, Department of Gastroenterology and Hepatology, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, Heilongjiang Province, China

Corresponding author: Shi-Zhu Jin, MD, PhD, Chief Doctor, Professor, Department of Gastroenterology and Hepatology, The Second Affiliated Hospital of Harbin Medical University, No. 246 Xuefu Road, Nangang District, Harbin 150086, Heilongjiang Province, China. drshizhujin@hrbmu.edu.cn

Abstract

There is a wide range of oesophageal diseases, the most general of which are inflammation, injury and tumours, and treatment methods are constantly being developed and updated. With an increasingly comprehensive understanding of stem cells and their characteristics of multilineage differentiation, self-renewal and homing as well as the combination of stem cells with regenerative medicine, tissue engineering and gene therapy, stem cells are playing an important role in the treatment of a variety of diseases. Mesenchymal stem cells have many advantages and are most commonly applied; however, most of these applications have been in experimental studies, with few related clinical trials for comparison. Therefore, the methods, positive significance and limitations of stem cells in the treatment of oesophageal diseases remain incompletely understood. Thus, the purpose of this paper is to review the current literature and summarize the efficacy of stem cells in the treatment of oesophageal diseases, including oesophageal ulceration, acute radiation-induced oesophageal injury, corrosive oesophageal injury, oesophageal stricture formation after endoscopic submucosal dissection and oesophageal reconstruction, as well as gene therapy for oesophageal cancer.

Key words: Stem cells; Oesophageal diseases; Differentiative capacity; Regenerative medicine; Tissue engineering; Gene therapy

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Core tip: Stem cells have many characteristics and can be used to treat various diseases. Currently, the use of stem cells for the treatment of oesophageal diseases is developing but is still not very common. Therefore, this paper summarizes the relevant literature on stem cell therapy for oesophageal diseases, including oesophageal ulceration, acute radiation-induced oesophageal injury, corrosive oesophageal injury, oesophageal stricture formation after endoscopic submucosal dissection and oesophageal reconstruction, as well as gene therapy for oesophageal cancer, to promote better the development of stem cell therapy for oesophageal diseases.

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INTRODUCTION

There are a wide variety of oesophageal diseases, including mainly inflammation, tumours and injury. Treatment methods include drugs, endoscopic treatment and surgery^[1]. With the development of stem cell-related research and technology, stem cells have gained increasing attention in the context of treating various diseases^[2].

By definition, stem cells have the capacity for multilineage differentiation and self-renewal. They can differentiate into many specific types of cells *in vivo*^[3]. Stem cells can divide into totipotent, pluripotent, multipotent and unipotent stem cells according to their differentiation potential. Totipotent stem cells can differentiate into any kind of cells, and pluripotent stem cells can differentiate into cells of all three germ layers. Pluripotent stem cells can differentiate into many kinds of cells, but they may not cover all cells of one germ layer, and unipotent cells can only differentiate into one type of cell^[4-6]. Stem cells can be divided into embryonic stem cells and adult stem cells according to their source. Embryonic stem cells at the morula stage, which are a kind of totipotent stem cells, have the differentiation potential to form a complete individual. With embryonic growth, the potential of stem cells continues to decline from totipotency to pluripotency^[7]. Adult stem cells are undifferentiated cells existing in a kind of differentiated tissue that can self-renew and specialize to form cells that make up this type of tissue. Adult stem cells can include pluripotent stem cells and unipotent stem cells^[6]. For example, haematopoietic stem cells are the most characteristic pluripotent stem cells and can differentiate into at least 12 kinds of blood cells^[8]. Mesenchymal stem cells (MSCs) can differentiate into a variety of mesodermal cells (such as bone, cartilage, muscle, and fat cells) and other blastodermal cells (such as neurons)^[9].

Currently, MSCs are studied the most intensely and used the most widely. MSCs are relatively abundant and easy to isolate and culture. The main sources include adult bone marrow, umbilical cord or placental blood and adipose tissue, the latter of which is being increasingly developed and used as a source^[10]. MSCs can also be isolated from the periosteum, skeletal muscle, teeth and other tissues^[11,12]. Isolated MSCs can be used to treat tissue and organ damage and functional failure. MSCs have a powerful proliferation ability and multidirectional differentiation potential and can differentiate into osteoblasts, chondrocytes, adipocytes, liver cells, muscle cells, stromal cells and other cells under appropriate conditions *in vivo* or *in vitro*^[13]. Stem cells can also be used as carriers for gene therapies. In particular, MSCs are the most widely used for this purpose. They can not only be easily transfected with exogenous genes but can also express the protein of exogenous genes and retain their own phenotype after the introduction of exogenous genes^[14]. This characteristic, combined with the multilineage differentiation potential of MSCs, renders MSCs potentially ideal target cells for gene therapy. MSCs have low immunogenicity and can reduce the immune exclusion effect during cell transplantation^[15]. Currently, stem cells can be cultured and isolated artificially *in vitro* according to certain purposes, and various cells, tissues and organs can be constructed using stem cells as a source for transplantation. Stem cells also exhibit homing; that is, under the influence of many factors, stem cells will migrate in a directional manner^[16]. It is widely believed that the mechanism is based on the release of some factors from the site of injury, which bind to receptors for these factors on the surface of stem cells^[17]. This characteristic allows stem cells to serve as a carrier of many therapeutic agents (Figure 1).

Stem cells can be effective in the treatment of many diseases, such as cardiovascular diseases, nervous system diseases, bone and cartilage diseases and inflammatory diseases. However, stem cells are not commonly used in the treatment of the oesophageal diseases. The mechanism of using stem cells for the treatment of some common diseases of the oesophagus can be similar to that applied in the treatment of other diseases. Based on the characteristics of the oesophagus itself, stem cells could play an even greater role. The following describes the use of stem cells for the treatment of different oesophageal diseases (Table 1).

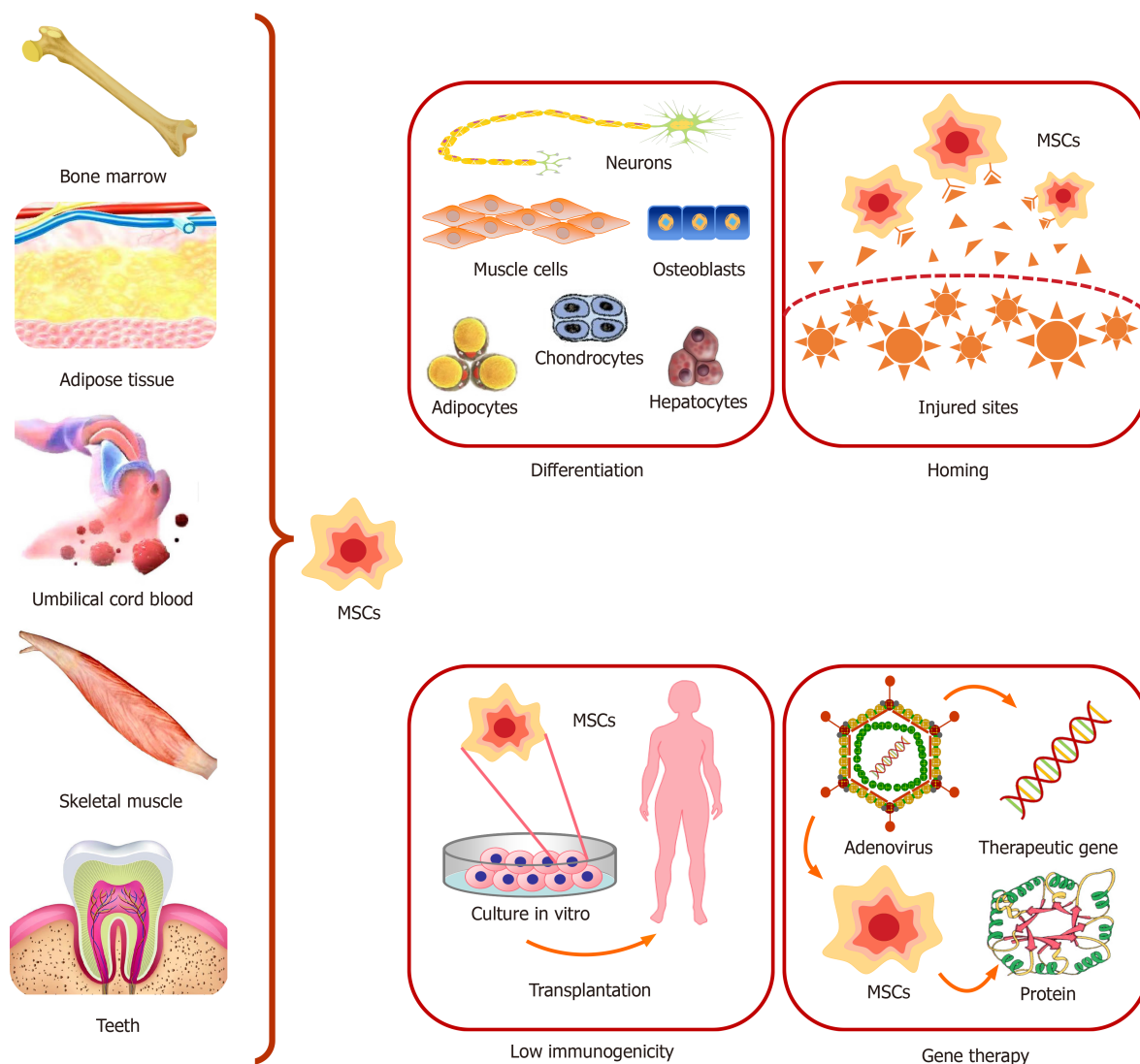


Figure 1 Sources and characteristics of mesenchymal stem cells. Mesenchymal stem cells (MSCs) have a wide range of sources, including adult bone marrow, umbilical cord or placental blood, adipose tissue, skeletal muscle, teeth and other tissues. MSCs have the capacity for multilineage differentiation and self-renewal. They can differentiate into neurons, muscle cells, osteoblasts, chondrocytes, adipocytes, hepatocytes and so on under appropriate conditions. MSCs have the characteristic of homing, the mechanism of which is widely believed to be that sites of injury release various factors, and there are receptors for these factors on the surface of MSCs. MSCs have low immunogenicity and can be cultured and isolated artificially *in vitro* for transplantation. MSCs can also be used as carriers for gene therapy. MSCs can be transfected with therapeutic genes and express the protein of exogenous genes well.

OESOPHAGEAL ULCERATION

Oesophageal ulcers are mostly caused by gastrointestinal reflux disease^[18]. The incidence of gastroesophageal reflux disease has increased significantly in the past decade^[19]. An ulcer is a defect in the mucosa that can deeply penetrate or even perforate the muscle layer. It is generally caused by ischaemia, oxygen radical formation or nutritional transport blockage. Ulcer tissue accumulates a variety of cytokines released by immune cells that play a complex role in various stages of ulcer recovery, including cell proliferation, re-epithelialization, neovascularization and scar formation. The natural recovery of ulcers consists of the development of surrounding cells towards the centre of the ulcer site and reconstruction of the mucosa. However, adult stem cells derived from bone marrow have the ability to differentiate into mature epithelium, which can fill the ulcer area with epithelium and accelerate the process of re-epithelialization^[20,21].

Okamoto *et al*^[22] transplanted bone marrow cells from male donors into four female patients who needed transplantation treatment due to haematological diseases. Epithelial tissue biopsy samples were collected from the recipient's digestive tract through gastroenteroscopy. With immunohistochemistry and fluorescence *in situ* hybridization, it could be determined that there were donor-derived cells in the recipient's epithelial tissue, most of which were epithelial cells and not inflammatory

Table 1 Related stem cell transplantation experiments

Stem cells sources	Transplant recipients	Transplant methods	Results	Ref.
Bone marrow cells from male human donors	Four female human recipients	Bone marrow transplantation	Regeneration of gastrointestinal epithelia	[22]
High K19-expressing MSCs from bone marrow of mice	Mice, <i>H. felis</i> infected mice	Gastric wall injection, blastocyst injection	Contributed to gastric epithelial regeneration and repair.	[23]
MSCs from bone marrow of male rats	Female rats with gastric ulcers	Gastric wall injection surrounding the ulcer	Acceleration of gastric ulcer healing	[24]
MSC sheets from inguinal fat tissue of rabbits	Rabbits with oral mucosal ulcers	MSC sheets transplanted onto mucosal ulceration	Full-thickness mucosal healing and complete basal cell coverage	[26]
Bone marrow cells from mice	Mice with radiation-induced oesophageal injury	Intravenous injection	Repopulation of the irradiated oesophageal squamous epithelium	[32]
DPSCs from rats	Rats with acute radiation-induced oesophageal injury	Intravenous injection (tail vein)	Healing of tissue damage and improvement the oesophageal function	[34]
MSCs from bone marrow of rats	Rats with oesophageal lye burn	Intravenous injection (tail vein)	Differentiation to epithelial and muscle cells	[37]
Double-layered ADSC sheets from the abdominal subcutaneous fat of pigs	Pigs treated with hemi-circumferential ESD	ADSC sheets placed on the wound site with endoscope	Reduced degree of oesophageal stricture and fibrosis development	[47]
CM of AMSCs from the foetal membrane of pregnant women	Pig treated with semi-circumferential ESD	CM gel applied on the wound site with endoscope	Reduced oesophageal fibrosis and inflammation	[48]
MSCs from bone marrow of pigs	Pigs for circumferential replacement of oesophagus	MSC-seeded matrix for circumferential Replacement of oesophagus	Acceleration of epithelial and muscle cell regeneration	[56]
MSCs from bone marrow of rats	Rats for circumferential replacement of oesophagus	MSC-seeded decellularized oesophagus for orthotopic replacement	Regeneration of functional epithelium, muscle fibres, nerves and vasculature	[57]
MSCs from adipose tissue of pigs	Pigs for full thickness circumferential resection of oesophagus	MSC-seeded synthetic grafts implanted into oesophagus	Regrowth of mucosa, submucosa, and smooth muscle layers and blood vessels	[59]
MSCs from bone marrow of human donors	Rats for interposition procedure between the oesophagus and stomach	MSCs and other cells constructing multicellular artificial oesophagus with bio-3D printing transplanted into oesophagus and stomach	Full coverage of inner luminal surface by epithelial cells	[60]
MSCs from bone marrow of human donors, then MSCs transduced with <i>IFN-β</i> gene	Rats inoculated with melanoma cells and MSCs	Intravenous injection (tail vein)	Proliferation of MSCs in tumours and inhibition of malignant cell growth	[66]
MSCs transduced with <i>IFN-α</i> gene	Mice inoculated with melanoma cells	Intramuscular injection	Decrease in tumour cell proliferation and induction of tumour cell apoptosis	[67]
MSCs from bone marrow of human donors, then MSCs transduced with <i>IFN-λ</i> gene	Mice injected with H460 cancer cells	Subcutaneous injection	Induction of tissue necrosis and inhibition of tumour cell growth in lung metastases	[70]
MSCs from bone marrow of human donors, then MSCs modified with <i>TRAIL</i> gene	Mice injected with Eca-109 cancer cells	Directly injection into tumour	Induction of Eca-109 oesophageal cancer cell apoptosis	[72]
MSCs from bone marrow of rats, then MSCs transfected with <i>TRAIL</i> gene	Mice injected with B16F10 cancer cells	Intravenous injection (tail vein)	Reduction of lung metastases and induction of tumour cell apoptosis	[62]
MSCs from adipose tissue of human donors, then MSCs transfected with <i>TRAIL</i> gene	Mice injected with HeLa cells	Flank injection, tumour injection	Inhibition of tumour cell growth	[73]

ADSC: Adipose-derived stromal cell; AMSCs: Amniotic mesenchymal stem cells; CM: Conditional medium; DPSCs: Dental pulp stem cells; ESD: Oesophagic submucosal division; *H. felis*: *Helicobacter felis*; IFN: Interferon; MSCs: Mesenchymal stem cells; TRAIL: Tumour necrosis factor related apoptosis-inducing ligand.

cells[22]. Okumura *et al*[23] demonstrated that MSCs in bone marrow can play a role in mucosal re-epithelialization and repair.

Cytokeratins are a class of proteins that maintain the cellular structure of epithelial

cells. Keratin 19 (K19) is a cytokeratin and can be considered a marker of epithelial cells. Therefore, K19 can be used to identify the transformation of MSCs into epithelial cells. Okumura *et al*^[23] isolated and cultured MSCs with high K19 expression and injected them directly into the gastric wall of mice. After 24 h, MSCs were found to have filled the gastric mucosa. After 4 wk, the expression of specific markers of epithelial cells was found at the site of MSC injection^[23]. Hayashi *et al*^[24] injected rat MSCs into the stomach wall of rats, observed the recovery of gastric ulcers induced by acetic acid and detected the expression of vascular endothelial growth factor (VEGF) produced by the transplanted MSCs in the rats. VEGF is a kind of angiogenesis regulatory factor that can induce the formation of new blood vessels in granulation tissue and is of great significance for ulcer healing^[25]. The application of VEGF antibody can inhibit the therapeutic effect of MSCs on ulcers in a dose-dependent manner^[24]. Therefore, VEGF plays a significant role in promoting angiogenesis in the treatment of ulcers with MSCs. The mechanisms of gastric ulceration and oesophageal ulceration are similar, so the above experimental principle is also applicable to the oesophagus.

Compared with bone marrow-derived stem cells, adipose-derived stem cells (ASCs) are easier and less invasive to obtain and easier to isolate and culture. One study demonstrated that the use of ASC sheets accelerated the healing of oral mucosal ulcers^[26]. In many ischaemic models, ASCs have been shown to increase the capillary density and decrease the inflammatory response^[27]. ASCs can secrete paracrine factors that promote tissue healing^[28], and their differentiation potential is also conducive to the treatment of damaged tissues^[29].

ACUTE RADIATION-INDUCED OESOPHAGEAL INJURY

Radiation therapy for various cancers in the chest, especially lung cancer, will inevitably lead to radiation-induced oesophageal injury^[30]. However, the occurrence of radiation-induced oesophagitis will hinder the treatment of cancer, and there are very few drugs that can protect the oesophagus from radiation^[31]. Therefore, stem cell therapy constitutes an innovative and effective treatment strategy.

Epperly *et al*^[32] simulated a model of radiation-induced oesophageal injury with 30 Gy of radiation. After bone marrow cells were injected intravenously into the model mice, the cells migrated to the oesophageal lesions, differentiated into oesophageal squamous epithelial cells and improved the overall survival rate of the mice. In addition, dental pulp stem cells (DPSCs) are a type of MSC that are used to repair periodontal tissues. In fact, in addition to forming odontoblasts, they can also differentiate into adipose, bone, cartilage, muscle, vascular endothelial, liver and nerve cells, among others, through induction with different cytokines. The isolation and collection of DPSCs is highly non-invasive and inexpensive^[33]. Zhang *et al*^[34] placed iodine 125 (¹²⁵I) particles into a disposable ureteral lumen and introduced them into the oesophagus to create an acute radiation-induced oesophageal injury model. DPSCs cultured *in vitro* were injected into the experimental Sprague Dawley rats through the tail vein. Finally, it was demonstrated that DPSC transplantation was helpful for the treatment of acute radiation-induced oesophageal injury. DPSCs expanded *in vitro* can home to oesophageal lesions to proliferate and trans-differentiate into oesophageal stem cells^[34].

CORROSIVE OESOPHAGEAL INJURY

Corrosive oesophageal injury occurs rarely in adults as an accident, but it is very common among children due to the characteristics of the children themselves, especially in many developing countries, for which there are many social causes^[35]. The mucosal layer of the oesophagus is destroyed when it is exposed to corrosive substances. As the disease progresses, the damage invades the muscular layer. In severe cases, perforation occurs. Self-repair may eventually lead to fibrosis, stenosis and shortening of the oesophagus^[36]. Drugs can be effective to varying degrees, but they cannot lead to much improvement in cases of serious injury.

To test the application of stem cells, Kantarcioglu *et al*^[37] made a standard model of oesophageal caustic injury with lye in 65 Wistar rats. Bone marrow MSCs were obtained from the tibia and femur of rats and cultured *in vitro*. They were injected into the experimental rats through the tail vein. Finally, a histopathological evaluation was performed, including determination of submucosal collagen, mucosal muscle injury, intrinsic muscle injury and collagen deposition as well as calculation of the oesophageal stenosis index. Positron-emission tomography was used to observe the

homing behaviour of the stem cells. The results showed that the structure of the oesophagus was not completely restored, but the stem cells indeed showed homing and differentiation behaviour. The researchers speculated that the less than ideal treatment may be related to the number and location of stem cell injections^[37]. Bone marrow MSCs have the ability to home to damaged tissue and differentiate into various cell types. Pittenger *et al*^[13] and Okamoto *et al*^[22] proved that MSCs can differentiate into epithelial cells in the damaged gastrointestinal tract to promote repair. Oswald *et al*^[38] demonstrated experimentally that bone marrow MSCs can differentiate into endothelial cells *in vitro*, greatly promoting angiogenesis and therefore facilitating tissue repair.

OESOPHAGEAL STRICTURE FORMATION AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION

With the increasing number of patients with oesophageal cancer, endoscopic submucosal dissection (ESD) has become a mature treatment strategy, especially for early oesophageal cancer^[39,40]. However, ESD has many side effects, and the incidence of stricture formation due to the peeled mucosa is very high, especially when more than three-quarters of the oesophagus is stripped. Prophylactic endoscopic balloon dilatation and steroid hormones have traditionally been effective strategies for preventing oesophageal stricture formation, although these methods can cause discomfort and complications^[41]. Regenerative medicine has been widely recognized as a method of treating diseases using the body's own components^[42]. Due to the development of regenerative medicine, techniques using autologous epidermal cell sheet transplantation have been developed to treat stenosis^[43]. This technology preserves the adhesion molecules between cells so that the cells can remain linked together during transplantation and attach to damaged tissue^[44]. For example, cell sheets composed of oral mucosal cells can promote oesophageal epithelial regeneration after ESD^[45].

Adipose-derived stromal cells (ADSCs) are a type of adult stem cell that can differentiate into different types of cells and exert paracrine and angiogenic effects to facilitate tissue repair^[46]. In addition, ADSCs are easy to isolate. Perrod *et al*^[47] performed ADSC sheet transplantation into the oesophagus post-operatively. Compared with the control, ADSC transplantation reduced the incidence of severe stenosis 3 d post-operatively. In addition to stem cells themselves, various secretory factors produced during stem cell differentiation may also have positive effects. Mizushima *et al*^[48] speculated that the therapeutic effect of foetal membrane or amniotic MSC (AMSC) transplantation on various diseases may be attributed to the factors secreted by the AMSCs; thus, conditioned medium (CM) obtained from AMSCs was used to explore its therapeutic effect on post-ESD stenosis. The researchers isolated and cultured AMSCs from the foetal membrane during caesarean section in pregnant women who had provided consent and used them to prepare CM gel. The experiment utilized different gradients and frequencies of CM gel usage to compare the use of steroid drugs. The degree of oesophageal stenosis was assessed by calculating the lateral mucosal constriction rate and performing histological and immunohistochemical examinations. The results demonstrated that CM could reduce fibrosis and inflammation in the oesophagus after surgery^[48].

OESOPHAGEAL RECONSTRUCTION

Oesophageal replacement or resection is required in many diseases, such as long-gap oesophageal atresia, a congenital disease in children, and oesophageal cancer in adults that requires oesophagectomy. Traditionally, oesophageal tissue is often replaced by tissue from the stomach, jejunum and colon. Many post-operative complications, such as stenosis, reflux, delayed emptying, anastomotic fistula and dysfunction, are inevitable and reduce the quality of life to a large extent^[49-51]. On the basis of regenerative medicine technologies, the rise of tissue engineering has greatly improved the treatment of this kind of disease. Tissue engineering integrates engineering and life science and uses scaffolds or a combination of scaffolds and cells to reconstruct the structure or function of tissues or organs^[52]. Scaffolds can be acellular or seeded with cells. However, the transplantation of acellular scaffolds requires advanced materials, which are needed to support the regeneration of corresponding tissues, such as epithelium and muscle. In oesophageal applications, it is possible to seed epithelial cells on the scaffold in advance, which is helpful for epithelialization of the oesophagus, but the muscular layer is difficult to form^[53].

Although many experiments have successfully transplanted autologous smooth muscle cells into the oesophagus, their proliferation capacity is limited^[54].

Zani *et al*^[55] have suggested that stem cells can help with oesophageal regeneration. In a study by Catry *et al*^[56], MSCs promoted the therapeutic effect. They isolated MSCs from the posterior iliac crest by aspiration and cultured them *in vitro*; then, they compared the effect of a stem cell-seeded matrix with that of a non-stem cell-seeded matrix in full-layer oesophageal replacement. The results showed more epithelial cells in the early stage in the transplanted area of the oesophagus along with muscle cell regeneration in the experimental group with stem cells than in the control group without stem cells. Therefore, under the effect of stem cells, the process of epithelial and muscle cell regeneration will be accelerated^[56]. Sjöqvist *et al*^[57] successfully integrated bone marrow MSCs into acellular scaffolds to replace the oesophagus and proved that MSCs can differentiate into oesophageal-related cells. There has now been a clinical case of using tissue engineering to treat an oesophageal defect. The patient underwent commercial stent placement but did not recover as expected. The researchers used extracellular matrix and autologous plasma to help repair the oesophagus. The extracellular matrix can provide an environment for stem cell differentiation and attract and induce stem cells to promote organogenesis. When the stent was removed, endoscopic ultrasonography showed that the newly formed oesophageal wall contained the five normal structural layers. Furthermore, the new oesophagus also achieved a certain degree of functional recovery^[58].

In addition to MSCs, ASCs are easy to obtain and abundant in number and can play an important role in tissue engineering of the oesophagus. According to experiments in which ASCs successfully differentiated into smooth muscle cells, Wang *et al*^[54] implanted ASCs into the muscle layer of an acellular matrix, and the results showed that the ASCs attached to the muscle layer and achieved migration and proliferation. La Francesca *et al*^[59] placed scaffolds loaded with adipose-derived MSCs into a pig model of oesophagectomy, along with a physical stent supporting the oesophageal structure. Histological examination of the oesophagus and an evaluation of oesophageal stenosis were performed. After removal of the physical stent and scaffold, the formation of oesophageal mucosa and muscularis was observed, as was vascularization, and there was no oesophageal stricture formation^[59]. Currently, on the basis of tissue engineering technology, it is possible to use scaffold-free structures composed of a variety of cells to replace the oesophagus using biological 3D printing technology. In cell mixtures, the more MSCs, the better the structure and function of the oesophagus^[60].

GENE THERAPY FOR OESOPHAGEAL CANCER

Oesophageal cancer ranks fifth among the most common cancers in China. Worldwide, 60% of new cases of oesophageal cancer occur in China^[61]. Based on traditional treatment with surgery, radiotherapy and chemotherapy, gene therapy, which has been successfully applied in the treatment of many diseases, has been developed for oesophageal cancer. The function of the therapeutic gene depends on the efficacy of the delivery carrier, and effective delivery to the tumour site is key in gene therapy. Viral vectors were more commonly used in the past, but there were some side effects that could lead to systemic damage, and many new vectors have limited therapeutic effects due to their respective characteristics^[62]. MSCs can still maintain their original characteristics after being successfully transfected with exogenous genes and cultured *in vitro*. MSCs can successfully express exogenous gene products *in vitro* and secrete therapeutic proteins as carriers *in vivo*^[63]. MSCs have been proven to inhibit tumour cell proliferation and tumour angiogenesis by secreting soluble factors *in vitro*^[64]. There are higher levels of paracrine growth factors in tumour tissues than in normal tissues. The proliferation of MSCs requires the presence of these factors^[63]. Hu *et al*^[62] found that stromal cell-derived factor 1 may attract MSCs to migrate to the tumour microenvironment *in vitro*. Therefore, MSCs, being able to migrate to tumour tissues, are also considered to be good carriers for therapeutic genes and anti-tumour biological agents^[65].

Studený *et al*^[66] investigated the effect of MSCs transfected with the interferon β (IFN- β) gene on tumour tissue. Clinical trials have shown that the use of IFN is limited by the systemic maximum tolerable dose and cannot fully exert its anti-tumour effect. However, MSCs transfected with the IFN- β gene can preferentially localize to tumour tissues so that IFN- β is locally released and minimally affects other areas^[66]. MSCs with the IFN- α gene can regulate the activity of immune cells by secreting IFN- α in tumour tissue^[67]. IFN- λ can inhibit cancer cell proliferation by blocking the G1 phase of oesophageal cancer cells^[68]. Li *et al*^[69] found that adenovirus

carrying the IFN- λ gene can induce mitochondrial-mediated oesophageal cancer cell apoptosis in mice. Therefore, it is a feasible method to introduce the IFN- λ gene into stem cells to treat oesophageal cancer. Yang *et al.*^[70] verified that IFN- λ -modified MSCs inhibit the growth of tumour cells by activating the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) molecular pathway. TRAIL is a molecule that can induce the apoptosis of tumour cells, but its short half-life in plasma limits its wide application^[71]. Li *et al.*^[72] introduced the TRAIL gene into human bone marrow-derived MSCs by adenovirus vector and delivered the MSCs into mice by subcutaneous injection on the back. The results showed that the MSCs could induce the apoptosis of oesophageal tumour cells and inhibit the growth of tumour tissue through the expression of TRAIL. Non-viral vectors can also be used to transfect MSCs, which would have no viral interference with the treatment and could improve the targeting effect of MSCs^[62]. Human adipose-derived MSCs are also an effective tool for TRAIL gene therapy for cancer, and the material source is more advantageous^[73].

There are many other tumour-suppressing genes that can be introduced into MSCs for cancer treatment, such as IL-12, IL-24 and pigment epithelium-derived factor. However, few genes have been identified for treating oesophageal cancer, and these can be further developed in the future^[74-76]. There is some debate regarding the effect of stem cells on tumours. Some experiments have shown that MSCs can promote tumour growth, which may be due to different experimental designs, the immunosuppressive effect of stem cells themselves or some cytokines secreted by stem cells^[60].

PROSPECTS

There are still some areas that need to be developed and expanded in the treatment of oesophageal diseases. For example, stem cells can be used as gene carriers or drug carriers directly, and drugs can be released in a targeted manner depending on the function of stem cell homing. The combination of nanocarriers and MSCs will allow better control over the position and mode of drug release^[77]. Additionally, MSC-derived extracellular vesicles (EVs) have good prospects in regenerative medicine techniques^[78]. As phospholipid bilayer vesicles, EVs secreted by MSCs contain many substances, such as enzymes, signal molecules and RNA. There have been many experiments showing that the EVs of MSCs can alleviate or treat many diseases by transmitting the effects of MSCs, including inhibiting the inflammatory response, promoting cell proliferation and promoting angiogenesis and anti-apoptosis ability. Future strategies could include increasing the content of active molecules in EVs, targeting them to damaged tissues, evading the clearance system to improve the action time and using EVs for drug delivery to improve the therapeutic efficiency^[79]. However, there is still much to learn about stem cells. In continuing to explore the benefits of stem cells for treating disease, there are still many uncertain factors and possible risks. In a model of oesophagitis and intestinal metaplasia in female experimental rats, bone marrow stem cells from male rats were injected into the tail vein of the experimental rats. The Y chromosome from the male rat cells could be found in the oesophageal squamous epithelium and metaplasia columnar epithelial cells in the female experimental rats, although the possibility of cell fusion could not be ruled out. However, summarizing similar experimental studies, it is undeniable that stem cells can promote the formation of oesophageal epithelialization and oesophageal metaplasia. It is well known that oesophageal metaplasia is an important process in the formation of Barrett's oesophagus, and Barrett's oesophagus is a risk factor for oesophageal cancer^[80]. In addition, genetically modified MSCs can be used to treat tumours. However, it is controversial whether bone marrow MSCs inhibit or promote tumour tissue activity. Experiments have shown that bone marrow MSCs can inhibit tumour cell proliferation and promote tumour cell apoptosis *in vitro* but can promote tumour growth *in vivo*, which may be related to the promotion of tumour angiogenesis^[81].

CONCLUSION

In summary, the treatment of oesophageal diseases by stem cells can be based not only on their own characteristics, such as multilineage differentiation, self-renewal, low immunogenicity and homing capacity, for the recovery and reconstruction of oesophageal structure and function to a certain extent, but also on integration with other biotechnology, the combination of which has greater therapeutic efficacy than either component alone. Although there have been few clinical trials, the prospects of

stem cells in the treatment of oesophageal diseases are very promising. In addition, the function of stem cells has not yet been completely understood. In the process of stem cell development, there are still many unknown and uncertain factors to be explored.

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