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Review

The stem cells applications in sport injuries

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Abstract: A variety of injuries may occur in the human body during exercise or sport, including skin scratches, soft tissue sprains, dislocations, and fractures. These injuries, which are commonly referred to as "sport-induced," have the potential to result in further deterioration, including meniscal (cartilage) injury, ligament strain, muscle and tendon strain, or osteoarthritis. Such injuries can have significant implications for the health of athletes, with the potential to result in the economic or mental burdens for the athletes and their families. Stem cells exhibit a number of advantageous characteristics, including pluripotency, superior tissue regeneration capacity, and an excellent immunomodulatory effect. They are capable of repairing cell or tissue damage at the lesion site and exhibit excellent antioxidant and anti-inflammatory effects, which makes them a promising area of application in sport medicine. This review article presents a summary of the recent progress made in the application of stem cells in the treatment of sport injuries, along with an analysis of the underlying mechanisms involved; additionally, it addresses the current limitations of stem cell applications in the context of sport injuries, with the aim of providing insights that can inform future research and clinical practice in this field.

Keywords: stem cells; sport medicine; sport injuries; regenerative medicine; mechanism

1. Introduction

Sport can be defined as a kind of regular and conscious activity with the potential to enhance physical fitness, improve human health, and cultivate various psychological qualities. Additionally, scientific evidence has demonstrated that sport has the preventative and therapeutic effects on numerous diseases by regulating several crucial signaling pathways. It has been demonstrated that participation in high-intensity sports such as basketball or soccer is associated with an increased risk of sports injuries [1–3]. Sports injuries are defined as injuries caused by excessive use of the limbs, resulting in the impairment or physiological disorder of tissues or organs, such injuries can occur in multiple parts of the human body, including the skin, muscle, tendon, joint, bone, nerve, vessel, and even visceral organs. Such injuries can have significant economic and social consequences for the athletes or their families [4–6]. An epidemiological study demonstrated that several kinds of different sports including team sports, combat sports, racquet sports, and track and field, are associated with a higher prevalence rate of sports injuries; additionally, the data indicated that the knees and shoulders are the most susceptible body parts to damage [7]. A survey conducted by the National Collegiate Athletic Association demonstrated that the injury rate in men's football was 0.93%, with the most prevalent injuries being concussions, lateral ligament complex tears, and hamstring tears [8]; Lambert et al. reported that there was a higher prevalence of sport injuries in Olympic combat sports, it was found that ACL rupture, karate, shoulder dislocation, and shoulder rotator cuff injury were the longest time loss injuries; anterior cruciate ligament injuries, unspecific shoulder injuries, and elbow ligament injuries occurred highly in male athletes [9]; Lambert et al. reported that approximately 64% of athletes experienced at least one time injury during their exercise or training, the area with the highest frequency of injury occurrence was the lower extremities; furthermore, the incidence of the injuries occurring during training was higher than during competition in track and field athletes [10]. These aforementioned evidences demonstrated that sport injuries have a relatively high occurrence frequency in athletes, consequently, it is imperative to implement effective prevention and treatment strategies associated with these injuries.

Stem cells are one kind of multipotent cells that have been shown to have the excellent anti-inflammatory and immunoregulatory effects, and in vitro study demonstrated that stem cells have the ability to differentiate into multiple cell lineages, exhibit the promising application potentials in regenerative medicine [11]. In recent years, with the rapid development of stem cell technologies, stem cells have been successfully applied in the treatment of many human diseases, including neurological diseases, cardiovascular diseases, skeletal diseases, and renal diseases [12–15]. For example, Peruzzotti-Jametti et al. applied neural stem cells in animal models of central nervous system (CNS) diseases and found that neural stem cells had the better neural tissue repair ability which was regulated by extracellular vesicles mediated related signaling pathways [16]; Li et al. reported that allogeneic adipose-derived mesenchymal stem cells, when intravenously injected into a high-fat diet rabbit model, were observed that these special stem cells could alleviate the symptoms of the animal model by decreasing the blood lipids and alleviating atherosclerotic plaque [17]; Mamillapalli et al. administered intravenously uterine-derived cells via intravenous injection to mice with acute kidney injury, found that uterine-derived cells could increase the survival rate, and improve the renal tubular and vascular regeneration in mice with acute kidney injury [18]. Recently, there have also been many exciting stem cells applications of stem cells in sports injuries, including the preclinical and clinical applications of multiple types of mesenchymal stem cells, such as bone marrow mesenchymal stem cells, adipose stem cells and neural stem cells in ligament injuries, joint injuries and achilles tendon injuries. In this review, we summarized the recent advances in stem cell applications in sports injuries and their underlying mechanism; furthermore, we discussed the current application challenges and application limitations of stem cell application in sports injuries.

2. The clinical manifestation of sports injuries

Anatomical and physiological damage to human tissues or organs is a common occurrence during sports activities, the occurrence of sports injuries is closely associated with the sports events and the characteristics of technical and tactical sports; and the level of sports training, sports environment and sports conditions may also affect the occurrence of sports injuries. Sports injuries can be classified into joint or cartilage injury, skin injury, muscle and tendon injury, synovial injury, brain injury, vascular injury, and visceral injury according to the anatomy structure of human body [19]; and the clinical manifestations of sports injuries have been demonstrated to include abrasions, hemorrhages, sprains, contusions, dislocations, and fractures; a variety of risk factors have been identified as potential contributors to the occurrence of sports injuries, including insufficient training, poor physical fitness of athletes, incorrect movements, and lack of self-protection ability, inadequate pre-sports preparation activities before sport, lack of training to adapt to the environment, and improper organization of training and competition work have also been associated with an increased risk of injury [20,21].

The ankle joint, consisting of the distal tibia, fibula, and talus, is one of the most important weight-bearing joints in the human body. Ankle sprains are a common clinical condition with the highest incidence rate among joint and ligament injuries. Statistically, it has been reported that the ankle joints are particularly susceptible to sports injuries [22,23]. In the clinic, the symptoms of first-time sprains are often severe, acute pain and swelling in the ankle joint will be found in the damaged tissue; and the patients may experience a feeling of ankle dislocation, mild inversion of the ankle joint, and the presence of obvious tender points at the site of deformation of the lateral ligament of the ankle joint [24,25]. It is estimated that approximately 20% of athletes suffered from ankle sprain during sports activities, the main risk factors of ankle sprain are the high intensity and high volume of movement of basketball and soccer, and the pathogenesis of ankle sprain can be attributed to three main movements, including plantarflexion, adduction, and inversion [26].

Muscle and tendon injuries are another kind of injury caused by sports, including neck muscle sprains, acute and chronic lumbar muscle injuries; tendon ruptures in the supraspinatus, biceps brachii tendon, quadriceps femoris tendon, and achilles tendon [27]; the symptoms of muscle and tendon injuries include local pain, swelling, and tenderness, there is also the occasional subcutaneous hemorrhage; severely, the function will be weakened or lost when there was the muscle or tendon rupture [28–30]. It is inevitable that participation in sports will result in the occurrence of brain injury, the symptoms of such injuries include the blurred consciousness, loss of consciousness, and memory decline; the type of sports was the main risk factors in the occurrence of brain injury, especially, with the high-speed impact sports, including football, rugby, and ice hockey, has the higher probability of causing the brain injury. Traumatic brain injury has the potential to result in disability and cognitive impairment in children and young people, with the capacity to pose a significant threat to their lives [31,32]. Serious sports accidents have the potential to result in the visceral injuries, and if accompanied by damage to abdominal parenchymal organs or large blood vessels, it can lead to death from massive bleeding; when hollow organs are damaged and ruptured, it can lead to the development of serious abdominal infections, which can be life-threatening. Early and correct diagnosis and timely and appropriate treatment are the key to reducing mortality from abdominal trauma.

3. Introduction of stem cells

Stem cells are a type of multipotent cells with the ability to self-replication, they can differentiate into a variety of functional cells under certain conditions [33]. Stem cells have abundant sources, at present, the distribution of stem cells has been found in multiple parts of the human body, include brain, blood, bone marrow, umbilical cord, and skin, these cells have the potential to differentiate into multiple types of tissue cells, although their developmental potential is limited [34]; moreover, the differentiation potential of stem cells in different developmental stages of the human body were also various, these factors contribute to the diversity of stem cell sources and types. Classically, according to developmental stages, stem cells can be classified into embryonic stem cells and adult stem cells; additionally, stem cells can be further categorized according to their differentiation potential, stem cells can be classified into three subcategories, including totipotent stem cells, pluripotent stem cells, and unipotent stem cells [35,36].

One of the characteristics of stem cells is multidirectional differentiation potential. Stem cells are primitive and unspecialized cells that are not fully differentiated and have the potential to regenerate various tissues and organs [37]. This advantage of stem cells reflects the unique and irreplaceable superiority of stem cells, stem cells can differentiate into specific cell types under specific conditions to treat specific diseases, and have been successfully applied to treat various types of diseases, including neurological diseases [38,39], cardiovascular diseases [40], and kidney diseases [41].

Stem cells are capable of secreting a variety of substances, including soluble cytokines, chemokines, growth factors, microRNAs, proteases, and extracellular vesicles, these active substances could participate in the regulation of signaling pathways, tissue repair, and tissue regeneration [42–44].

Another application characteristic of stem cells is homing. Based on the homing ability of stem cells, stem cell transplantation has been widely used in the treatment of major diseases, including hematological diseases, immune-related diseases, and tumors. Normally, when our body's tissues and organs are damaged; a number of homing-related active factors are released, including chemokines, growth factors, and adhesion molecules, these homing related bioactive factors related to the homing are released to bind to the surface receptors of stem cells and to regulate the signaling pathways to guide stem cells spontaneously migrate to damaged tissues or damaged organs in the body [45–47].

With their distinctive regenerative capacity, multidirectional differentiation potential, and homing ability, stem cells have been facilitated their utilization in the treatment of various diseases. Currently, there are approximately ten thousand clinical trials are underway worldwide, covering for 8 major systemic diseases including neurological system diseases, endocrine system diseases, reproductive system diseases, autoimmune system diseases, cardiovascular and cerebrovascular system diseases, digestive system diseases, musculoskeletal system diseases, and circulatory system diseases, these trials demonstrate the great potential applications in the treatment of various diseases [48].

4. Stem cell applications in sports injuries

Stem cells are a type of pluripotent cells with the excellent multidirectional differentiation ability and immune regulation ability, they could secrete various kinds of growth factors, cytokines, and exosomes that can activate or regulate various signaling pathways [49,50]; and stem cells can also differentiate into multiple cell types, including neural cells, osteoblasts, chondrocytes, and skin cells, these cells can play an important role in the process of tissue repair and regeneration in alleviating or treating sports injuries [51]. There are many kinds of stem cells have been reported, including embryonic stem cells, bone marrow mesenchymal stem cells, adipose stem cells, umbilical cord mesenchymal stem cells; In fact, these stem cells have been applied in the treatment of a variety of sports injuries, including tendon injuries, ligament injuries, and muscle injuries; the application ways include direct surgical application, stem-cell-bearing sutures, and intravenous injection, these approaches have demonstrated the excellent repair ability and functional plasticity in sport injuries compared to the traditional methods. For example, Chiu et al. applied bone marrow-derived mesenchymal stem cells (BMSCs) in muscle contusion model to assess the effect on contusion injury, found that the administration of BMSCs led to an increase in regenerating myofibers were increased at the injury site, and improved the fast-twitch and tetanus strength in a muscle contusion model [52]; to evaluate the effects of BMMSCs of tendon injuries, Yu et al. isolated the exosomes from BMMSCs, encapsulated the exosomes into fibrin and injected the exosomes-modified fibrin into a rat model, the data demonstrated that the symptoms of the rats were significantly improved, several biochemical markers increased, including type I collagen and tenomodulin, demonstrated that BMMSCs-derived exosomes may be a potential therapeutic drug for tendon injuries [53]; and Iyer et al. validated the effects of mesenchymal stem cell (MSC) derived exosomes on a rat model of muscle injury, found that MSCs-derived exosomes could improve the skeletal muscle regeneration and accelerate recovery in rat model [54]. We summarized the recent research progress of stem cells preclinical applications in sports injuries, found that the application of stem cells mainly focused on tendon injuries, cartilage injuries, and meniscus injuries; the main types of animal models included human, mouse, rat, and rabbit; the types of stem cells included bone marrow mesenchymal stem cells (BMMSCs), adipose-derived stem cells (ADSCs), induced pluripotent stem cells (iPS), peripheral blood-derived mesenchymal stem cells (PBDMSCs), human umbilical cord mesenchymal stem cells (HUCMSCs), amniotic mesenchymal stem cells (AMSCs), tendon stem cells (TSCs), and urine-derived stem cells (UDSCs) (**Table 1** and **Figure 1**).

Table 1. The recent progress of stem cells preclinical applications in sport injuries.

Species	MSCs type	MSCs or derivative	Animal model	Therapeutic effects	The underlying mechanism	References
/	MSCs	Prrx1-expressing	Mouse	Bone, white adipose tissue and dermis repair	Wnt signaling	[55]
Human	BMMSCs	MSCs-conditioned medium	Rat	Promote tendon-bone healing	Smad 2/3 signaling pathway	[56]

Table 1. (*Continued*).

Species	MSCs type	MSCs or derivative	Animal model	Therapeutic effects	The underlying mechanism	References
Rat	BMMSCs	MSCs	Rat	Decreased apoptosis, promoted proliferation, and restored mitochondrial function.	/	[57]
Mouse	ADMSCs	Extracellular vesicles	Mouse	Promoted tendon anti-inflammatory gene expression and reduced mononuclear cell accumulation.	Toll-like receptor 4/NF-κB signaling pathway	[58]
Human	Kartogenin-preconditioned MSCs	Exosomes	Rat	Promote cartilage formation and collagen maturation.	/	[59]
Human	PDMSCs	Kartogenin-conjugated double-network hydrogel combined with stem cell	Rabbit	Promote chondrocyte differentiation	/	[60]
Human	UDSCs	MSCs	Canine	Increase bone volume/total volume and trabecular thickness	/	[61]
Human	TSCs	Micropattern silk fibroin film + MSCs	Rat	Improve the injured tendon	α 2β 1/FAK/PI3K/AKT signaling pathway	[62]
Human	TSCs	Acellular porcine achilles tendon patch + MSCs	Rat	Promote tendon-to-bone healing	/	[63]
Human	TSCs	Polydimethylsiloxane (PDMS) substrates + MSCs	Mouse	Improve tenogenesis capacity	Activate the integrin-αm	[64]
Mouse	Synovial MSCs	BMP-7 modified SMSCs-exos	Rat	Improve the pathological changes	promote synovial macrophages M2 polarization	[65]
Human	AMSCs	Cellular amniotic membrane scaffold + FGF-2-induced MSCs	Rabbit	Accelerate tendon-to-bone healing	/	[66]
Rat	BMMSCs	KGN-loaded BMSCs	Rat	Improve the organized structure	/	[67]
Human	ADSCs	Macro porous granular hydrogels + extracellular vesicles	Rat	Improve osteoporotic tendon-To-bone healing	Activate NF-κB signaling pathway	[68]
Mouse	BMMSCs	Runx2 overexpression MSCs	Rabbit	Improve the knee cartilage repair	/	[69]
Rat	BMMSCs + TSCs	The scaffold + MSCs	Rat	Improve tendon-to-bone repair	/	[70]
Human	AMSCs	MSCs encapsulating cartilage particles	Rabbit	Improve osteochondral defect repair	/	[71]
Human	HUCMSCs	Extracellular vesicles	Ovine	Improve tendon and tendon-to-bone repair	/	[72]
Rabbit	PBDMSCs	Demineralized cortical bone matrix + MSCs	Rabbit	Improve meniscal reconstruction	/	[73]
Mouse	BMMSCs	Exosomes	Mouse	Promote fibrocartilage regeneration	delivering miR-140	[74]
Rabbit	MSCs	Tenoinductive collagen biotextile + MSCs	Rabbit	Improve tendon-like tissue formation	/	[75]

Table 1. (*Continued*).

Species	MSCs type	MSCs or derivative	Animal model	Therapeutic effects	The underlying mechanism	References
Rabbit	ADSCs	Scaffold + adipose-derived stem cell	Rabbit	Improve bone regeneration, fibrocartilage formation	/	[76]
Rabbit	BMMSCs	Acellular tendon scaffold + BMMSCs	Rabbit	Promote the regeneration of cartilage layer	/	[77]
Human	ADSCs	Silk fibroin scaffolds + MSCs	Mouse	Increase bone formation	/	[78]
Human	MSCs and iPS	Hybrid implants + MSCs + iPS	Rat	Enhanced angiogenesis and neovascularization	/	[79]
Rat	BMMSCs	BMMSCs labeled with superparamagnetic iron oxide	Rat	Promote TBI healing	/	[80]

Abbreviations: MSCs, mesenchymal stem cells; BMMSCs, bone marrow mesenchymal stem cells; ADSCs, adipose-derived stem cells; iPS, induced pluripotent stem cells; PBDMSCs, peripheral blood-derived mesenchymal stem cells; HUCMSCs, human umbilical cord mesenchymal stem cells; AMSCs, amniotic mesenchymal stem cells; TSCs, tendon stem cells; UDSCs, urine-derived stem cells; NF-κB, nuclear factor kappa-B; PI3K, Phosphoinositide 3-Kinase; AKT, protein kinase B.

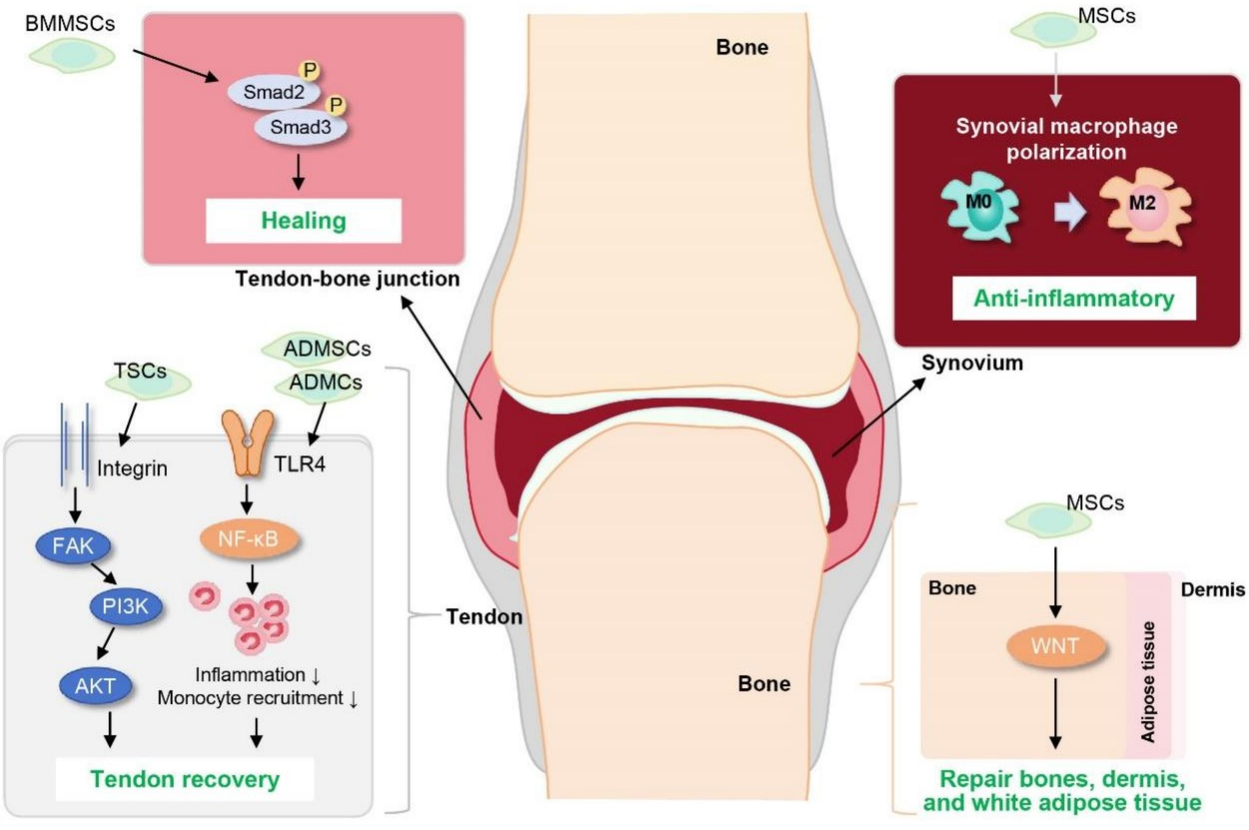

Figure 1. The summary of stem cells applications in sport injuries and the underlying mechanisms.

Several clinical applications of stem cells in sports injuries were also found. The collected data demonstrated there were seven randomized controlled trials of stem cell applications in sports injuries from 2019 to 2024 in six countries including Malaysia, Portugal, South Korea, Spain, Italy, and the USA; the trial period ranged from 6 weeks to 28 months; and the stem cell types included BMMSCs, adipose-derived stem cells, and peripheral blood stem cells; the application indications included knee chondral defects, knee osteoarthritis, and rotator cuff tears (**Table 2**).

Table 2. The clinical applications of stem cells in sport injuries.

The stage of trials	Country	Trials period	Stem cell type	Injury type	Therapeutic effect	Reference
Dual-center randomized controlled trial	Malaysia	24 months	PDSCs	Knee chondral defects	Increase mean IKDC scores and KOOS-pain subdomain scores	[81]
Controlled, double-blind clinical trial	Portugal	12 months	BMMSCs	Knee osteoarthritis	Improve the function and decrease symptoms	[82]
Randomized controlled trial	South Korea	28 months	MSCs	Varus knee osteoarthritis	Improve cartilage regeneration	[83]
Open-label, single-arm trial	Spain	12 months	ADSCs	Anterior cruciate ligament reconstruction	Improve knee function and healing/maturation	[84]
Comparative clinical trial	Italy	6 months	ADSCs	Knee osteoarthritis	Improve pain and functional outcomes	[85]
Double-blind, randomized, prospective Study	Spain	6 months	BMMSCs	Chronic patellar tendinopathy	Reduce pain and improve activity	[86]
Randomized, controlled clinical trial	USA	6 weeks	ADSCs	Partial-thickness rotator cuff tears	Increase mean ASES total scores	[87]

Abbreviations: PBSCs, peripheral blood stem cells; BMMSCs, bone marrow mesenchymal stem cells; MSCs, mesenchymal stem cells; ADSCs, adipose-derived stem cells; ASES scores, American shoulder and elbow surgeon’s score.

5. Conclusion and perspectives

Sports injuries are the various types of injuries that occur during the course of sports participation, they are the result of a complex interplay between multiple risk factors, including the level of sports skill, the technical difficulty, and the sports environment. Currently, the conventional methods of treating sports injuries include physical treatments, chemical treatments, and open and minimally invasive surgical treatments [88]; these physical treatments, chemical treatments, or open and minimally invasive surgical treatments represent a kind of passive repair approach, which facilitates the body in autonomous recovery rather than actively repairing the damaged tissues. Stem cells are a group of cells with pluripotent differentiation potential, they could be capable of differentiating into multiple types of somatic cells and secreting multiple factors to promote the injury tissue or injury cells to regenerate, and stem cells have the better immunoregulatory effect and low immunogenicity characteristic, can effectively improve the sports injuries while reducing the interference of side effects. Conversely, the differences in pluripotency and uncertainty in the differentiation direction of stem cells, have a significant impact on the application of stem cell in sports injuries. Currently, there are several application limitations that should be considered: (1) there are many kinds of stem cells, including BMMSCs, HUCMSCs, ADSCs, and TSCs have been applied in the treatment of sports injuries at both the preclinical and clinical stages, but the specific stem cell types, stem cell batches, and the different culture methods may result in the different characteristics of the stem cells, different levels of stem cell activity, and the different types and concentrations of growth factors secreted by the stem cells, these factors may become the main obstacles to the application of stem cells in sports injuries. Therefore, it is necessary to establish strict and unified standards for stem cell culture method, passage method, and stemness maintenance method. (2) Because the heterogeneity of stem cells, stem cells exhibit significant differences in proliferation, differentiation, pluripotency, and growth factor secretion, and these differences may influence the therapeutic effect of stem cells in sports injuries. Establishing specific screening methods based on specific biomarkers to distinguish differentiated cells may be a potential solution. (3) The applications of stem cells in conjunction with the biomimetic scaffolds in sports injuries have made great progress, but the degradation products of the biomimetic scaffolds remain uncertain and it may be the potentially toxic or inflammatory, it is necessary to establish a series of preclinical and clinical safety evaluation methods and conduct a series of preclinical and clinical safety evaluations for applications of stem cells in conjunction with the biomimetic scaffolds. (4) Despite the abundance of preclinical and clinical evidence demonstrating that the effects of stem cells on sports injuries and no significant adverse effects have not been reported. However, systematic and reliable clinical evidence is also lacking, and the biosafety of stem cell transplantation is also needs to pay the high attention.

In conclusion, we provided a summary of the clinical manifestations of sports injuries, the recent preclinical applications and clinical applications of stem cells in sports injuries, and discussed the various application limitations of these applications. It was found that stem cells have great potential for application in sports injuries. With the establishment of standard culture method, passage method, specific screening methods based on specific biomarkers to distinguish differentiated cells, preclinical and clinical safety evaluation methods, the application of stem cells in sports injuries will make great progress.

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