

Article

Stem cells application in frailty

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Abstract: Frailty can be defined as a systematic physiological decline that typically occurs in the nervous, muscular, metabolic, and immune systems of the older people. A multitude of risk factors have been identified to contribute to cause or exacerbate frailty, these risk factors lead to a heightened complexity and difficulty in preventing and treating frailty, which seriously threatens the health and well-being of the elderly people. Because of the unique characteristic of stem cells, including being a convenient source, low immunogenicity, and multi-directional differentiation potential, considerable advancements have been made in the field of frailty research. In this review, we summarized the impacts of the main risk factors, including genetic factors, ageing, sex differences, polypharmacy, malnutrition and unhealthy lifestyles in the onset and progression of frailty, provided an overview of the recent research progress in preclinical and clinical applications of stem cells in frailty, and discussed application limitations of stem cells in frailty and proposed the possible solutions. It was concluded that stem cells represent an ideal potential treatment method for frailty, offering significant advantages in terms of convenience, immunogenicity, and pluripotency.

Keywords: frailty; stem cells; risk factors; ageing; preclinical application; clinical application

1. Introduction

Frailty is a clinically significant syndrome that affects the older people, its main features include sarcopenia, inflammation, and loss of daily activity; frailty typically affects multiple physical systems in the body, including the nervous system, metabolic system, endocrine system, and immune system [1–3]. The etiology of frailty is multifaceted, encompassing genetic factors, aging, sex differences, and the potential adverse effects of polypharmacy [4–6]. It is increasingly recognized that multiple risk factors may coexist and contribute to the onset and progression of frailty, leading to the complexity of frailty. Diagnosis and intervention at the early stage of frailty could delay the onset and progression of frailty [7].

Statistics data demonstrated that the number of individuals aged 65 and above will increase by approximately 5 times in 2050 in the world, compared to 2004 figures [8]; and there is a strong correlation between the aging population and the rising prevalence of frailty [9]. Global statistical results demonstrated that the

prevalence of frailty ranges from 4% to 59% worldwide; especially, in developed countries, where economic prosperity and a more favorable lifestyle are more prevalent, the prevalence of frailty is significantly lower than in developing countries [10]. For example, Halloran, et al. investigated 8504 participants aged 65 and above in Ireland (a developed country), found that the prevalence rate of frailty reached 26.5% [11]; similarly, Takele, et al reported that the prevalence of frailty was 39% in a total of 607 participants in Ethiopia (a developing country) [12]. It has been reported that 10% of the community-dwelling elderly population in China aged 60 and above are affected by frailty, this proportion increases to approximately 15% in the 75–84 age group, 25% in the 85-year-old age group, and 30% in the hospitalized elderly population, respectively [13]. China is the most populous country in the world with a population of 1.3 billion, it is therefore inevitable that a significant proportion of this population will be elderly individuals suffering from frailty, those who are frail and under stress are at risk of developing a series of clinical adverse events, which can result in a considerable economic burden on both the patients and their families.

Stem cells are a type of cell which derived from embryos, fetuses, or adults' tissues that have unlimited self-renewal, proliferation, and differentiation abilities under certain conditions. Stem cells are typically classified into three categories based on their developmental potential: totipotent stem cells (all cells before 32 cells from fertilized egg to cleavage stage, such as embryonic stem cells), pluripotent stem cells (having the ability to generate multiple types of cells, but losing the ability to develop into a complete individual, such as bone marrow mesenchymal stem cells), and unipotent stem cells (can only differentiate into or produce one type of cells, such as satellite cells in muscles) according to its different developmental potential. It has the potential to differentiate into a variety of multiple functional cells, including nerve cells [14], cardiomyocytes [15], muscle cells [16] and nephrocytes [17]. With the rapid development of regenerative medicine, stem cells and their related technologies have been employed in numerous fields, with some applications advancing to the clinical stage. The distinctive properties of pluripotency and immunogenicity inherent to stem cells offer promising avenues for their utilization in the context of frailty. The aim of this review is to present an overview of the impact of risk factors on the onset and progression of frailty, as well as the advancement of preclinical and clinical applications of stem cells in frailty, it is our hope that this review will offer insights that can inform the development of strategies for the prevention and treatment of frailty.

2. Survey methodology

This review summarized the research articles from PubMed, Scopus, Embase, ScienceDirect, and Web of Science databases over the past five years.

3. The onset and progression of frailty

Evidences demonstrated that the onset and progression of frailty are the result of the interaction of numerous risk factors including genetic factors, aging, sex, polypharmacy, unhealthy lifestyles, and malnutrition. These risk factors do not exist

alone, they often co-exist, collectively influencing the progression of frailty and contributing to its complexity.

3.1. Genetic factors and frailty

Genetic polymorphism may influence the clinical presentation of frailty. A number of genes have been identified as being associated with frailty, these include interleukin 6 (IL-6) [18], C-X-C motif chemotactic factor 10 (CXCL10) [19], growth differentiation factor-15 (GDF15) [20], calmodulin/senescence marker protein 30 (RGN/SMP30) [21], Calreticulin (CRT) [21], angiotensinogen (AGT) [21], brain-derived neurotrophin (BDNF) [22,23], recombinant human pregranule protein (PGRN) [21], α -Klotho gene (KL) [21], fibroblast growth factor 23 (FGF23) [21], fibroblast growth factor 21 (FGF21) [21], keratin 18 (KRT18) [21] and microRNA (miRNA) [24]. The aforementioned genes regulate the relevant signaling pathways, thereby influencing an individual's susceptibility to frailty. For example, Pansarasa et al. [25] investigated the role of inflammatory cytokines, including IL1 β , IL2, IL6, IL8, IL12 p70, TNF α , and IFN γ in individuals with and without frailty, found that the levels of IL1 β , IL6, and tumor necrosis factor alpha (TNF α) in plasma of frail people were significantly increased, this evidence substantiates the assertion that inflammatory cytokines IL1 β , IL6 and TNF α play a pivotal role in the development of frailty. The elucidation of the impact of IL1 β , IL6 and TNF α will facilitate a deeper understanding of the aetiology of frailty [25]. Sanz-Ros., et al. obtained the adipose mesenchymal stem cells (ADSCs) from young mice aged between three and six months, and isolated the extracellular vehicles (EVs) from ADSCs, and found that EVs derived from ADSCs could alleviate the process of frailty, decrease oxidative stress and inflammation, and alter metabolites in older mice aged between 20 and 24 months; subsequent analysis demonstrated that multiple miRNAs were expressed at elevated levels in young ADSC-sEVs relative to sEVs derived from aged mice; additionally, three miRNA (miR-125b-5p, miR-let7c-5p, and miR-214-3p) were identified as playing a crucial role in progression of frailty [26]. Thomaz, et al. identified and compared the various types of microRNAs in individuals with and without frailty. It was observed that 53 distinct miRNAs exhibited significantly higher expression levels in individuals with frailty compared to those without frailty. Among these, miR-103a-3p, miR-598-3p, and miR-130a-3p were found to be particularly associated with frailty and aging [27]. The data suggest that microRNAs may represent a potential genetic factor for prevention or treatment of frailty.

3.2. Aging and frailty

Aging is considered one of the main risk factors for the progression of frailty. It is typical for degeneration and reserve capacity of organs due to age in humans; and for the incidence of frailty to increase exponentially with age. Gerd Ahlström, et al. investigated 7936 individuals aged 55 and above with intellectual disabilities, results demonstrated that there was a strong correlation between aging and frailty [28], and as a consequence of the aging process, there is a decline in the sense of smell and taste. This is attributable to the degenerative processes affecting the olfactory and taste organs, which are regulated by hormonal and inflammatory factors.

Consequently, appetite is diminished, a condition medically defined as anorexia of aging. This may subsequently result in a reduction in body weight and muscle mass; consequently, anorexia of aging is recognized as a direct risk factor for frailty [29]. Catharine et al. [30] investigated 3505 individuals aged 60 and above by a 12-item questionnaire to examine relationship between aging and frailty, and found that individuals aged 60 and above who have the positive attitude had a lower probability of developing frailty, these results suggested that the positive attitude may contribute to healthier lifestyle choices and dietary habits, which in turn may enhance the body's metabolism, potentially reducing the risk of developing frailty. Lin et al. [31] investigated the demographic data, aging-related physical conditions, and body functions of the 1072 elderly individuals aged 60 or above in Lianyungang City, China. They found that the prevalence of frailty among this elderly population was 13.8% during the 2020–2021, These results demonstrated that age is an independent risk factor for frailty, and aging including sarcopenia and nutrition could affect the process of frailty.

3.3. Sex differences and frailty

Evidence also indicated that sex is a risk factor for frailty. A substantial body of evidence demonstrated that women are more prone to developing frailty at various life stages [32,33]; additionally, prevalence of frailty is higher in women than in men [34,35]. Interestingly, despite this, women have a lower mortality risk associated with frailty compared to men of the same age [36,37]. However, the underlying mechanisms responsible for these observed differences remain unclear. To elucidate the mechanisms underlying the higher prevalence of frailty in females, Leonard, et al. analyzed the immune cell subpopulations, including T cells, B cells, NK cells, monocytes, and neutrophils in peripheral blood from 289 elderly people (aged between 60 and 87 years old). They found that women with frailty had a higher total amount monocytes and CD16-monocytes, lower numbers of CD56 + T cells and CD4 + TemRA cells compared to men with frailty; these data indicated that immune subpopulation-related immune mechanisms may play a significant role in sex-specific frailty [38]. Natasha et al. [39] analyzed and compared the transcriptome of peripheral blood mononuclear cells from females with frailty, non-frail females, males with frailty and non-frail males by RNA-sequencing. The results demonstrated that there were many differentially expressed genes in the four different groups, including 86 differentially expressed genes between females with frailty and males with frailty. Furthermore, 93 canonical pathways were identified between the females with frailty group and males with frailty group, with additional research that confirmed that musculoskeletal, metabolic, immunological, and inflammatory mechanisms also contribute to the observed sex differences in frailty.

3.4. Polypharmacy and frailty

Polypharmacy is typically defined as the concurrent use of five or more medications by a single patient. In clinical practice, the complexity of the process is evident, as polypharmacy is involved in the interactions between drugs, drug-disease interactions, and their side effects in elderly individuals; consequently,

polypharmacy is closely related to frailty. In order to gain insight into the relationship between polypharmacy and frailty, M. Gutiérrez-Valencia, et al. conducted a comprehensive review of 25 publications from MEDLINE, CINAHL, the Cochrane Database and PsycINFO, found that 16 cross-sectional analyses and 5 longitudinal analyses and reported that there was a significant association between polypharmacy and frailty; and they observed that the degree of frailty was correlated with the number of medications taken by patients. Based on these findings, they proposed that polypharmacy should be assessed before application in frail individuals [40]. Hiroshi Kimura, et al. assessed and analyzed the number of prescribed medications, the relationship between the number of medications and frailty, and the relationship between the number of the medications and the incidence of frailty in 337 patients on hemodialysis. They found that the number of concurrent medications was positively correlated with the degree and incidence of frailty in hemodialysis patients, and appropriately reducing the number of medications could potentially lead to a reduction in the degree and incidence of frailty [41].

3.5. Malnutrition and frailty

It has been documented that malnutrition represents a significant risk factor for frailty and one kind of characteristics of common aging syndromes. Malnutrition in a clinical setting may lead to an elevated risk of hospitalization, infection, and mortality; it can impose a significant economic burden on the elderly population and their families. Indeed, there are a lot of evidence has demonstrated that malnutrition could result in frailty. For example, Adham M Karim, et al. collected and analyzed the basic data of inpatient samples from 2012 to 2015 using multivariable regression analysis to assess the correlations between malnutrition, CLTI and frailty. They found that CLTI patients were accompanied with malnutrition or frailty, malnutrition regulation may have the beneficial effect on the prevention of CLTI and frailty [42]; Yogesh, et al. investigated the prevalence of frailty and malnutrition risk in a cohort of 263 patients aged 65 and above in Australia, and found that there were 33.5% of the patients exhibited both frailty and malnutrition risk concurrently. Additionally, the study identified an overlap between frailty and malnutrition in elderly hospitalized patients [43]. In China, Liu et al. [44] also observed a higher prevalence of poor nutritional status and physical frailty in nursing homes in Changsha. Their findings suggest that nutritional status may contribute to the incidence of physical frailty.

3.6. Unhealthy lifestyle and frailty

An unhealthy lifestyle may also increase the risk of developing frailty or accelerate the progression of frailty. Generally, unhealthy lifestyle factors include smoking, excessive alcohol consumption, lack of exercise, and poor personal hygiene. These unhealthy lifestyle choices can have adverse effects on the cardiovascular, respiratory, and nervous systems, which may subsequently contribute to the development of frailty. For example, Lv et al. [45] found that the genetic predisposition to smoking was highly correlated to frailty. The genetic results demonstrated that there was a suggestive relationship between alcohol consumption

and frailty. There data indicated that smoking was a causal risk factor for frailty. Heidi et al. [46] conveyed that relationship between frailty and substance use, including alcohol, tobacco, and drugs, in seven regions of the United States between 2016 and 2019. The data demonstrated that women and older people infected with HIV who smoked cigarettes were more likely to experience frailty. Furthermore, smoking was associated with a 61% increased risk of frailty in the HIV-positive population. In particular, Fu et al. [47] recruited and analyzed 2703 older adults aged 60 or above from 2011 to 2014. They found that cotinine levels in serum were highly correlated with frailty. Furthermore, they demonstrated that reducing exposure to secondhand smoke could decrease the risk of frailty and slow the process of frailty. Mulasso et al. [48] demonstrated that multicomponent exercise has a beneficial impact on frail and pre-frail individuals, particularly in comparison to those who do not engage in exercise or who have limited exercise routines. These data demonstrated that an unhealthy lifestyle could result in frailty. In construct, to reduce smoking and alcohol consumption, increase exercise, and maintaining a good personal hygiene situation might improve the frailty.

4. Preclinical and clinical applications of stem cell in frailty

Aging is an inevitable physiological process in the human body, a substantial body of evidence demonstrated that aging is closely related to frailty [49–51]. Normally, as a principal factor in the aging process, senescent cells could secrete the factors of senescence-associated secretory phenotypes (SASP), including inflammatory cytokines, chemokines, growth factors and proteases. These inflammatory factors play a role in signaling mechanisms that regulate tissue and organ aging. Furthermore, it is possible that aging-related genome instability, DNA damage, epigenetic alternations, oxidative stress, inflammation, mitochondrial dysregulation, and stem cell exhaustion may also play an important role in the development of frailty. Mesenchymal stem cells are a type of cells that possess the characteristics of self-renewal and immunogenicity, they offer numerous potential applications due to their unique properties: (1) possess the capacity to replace damaged tissues or damaged cells in the body; (2) secrete a range of various proteins, growth factors and cytokines that promote cell proliferation and to inhibit cell apoptosis; (3) exert an immunomodulatory effect.

A substantial body of evidence has emerged indicating that stem cells may offer a promising avenue for therapeutic intervention in a range of conditions associated with frailty, including Parkinson's disease [52], traumatic brain injury [53], spinal cord injury [54], cardiovascular disease [55], stroke [56], and atherosclerosis [57]. These findings suggest that stem cells may have a significant potential for addressing the complex and multifaceted nature of frailty. For example, Li et al. [58] demonstrated that stem cells derived from human menstrual blood could enhance motor functions, maintain the number of dopaminergic neurons, and reduce the expression of pro-inflammatory factors in a rat model of PD, and further confirmed that the PI3K/Akt and MAPK signaling pathways play an important role in the treatment. Ning et al. [59] analyzed the effects of bone marrow derived-mesenchymal stem cells- derived exosomes from rats with acute myocardial

infarction. They found that after bone marrow-derived mesenchymal stem cells-derived exosomes were pretreated with atorvastatin, the inflammatory response was attenuated and the infarct size in rats was reduced by regulating the miR-139-3p/Stat1 pathway in macrophages. In a recent study, Egea et al. [60] provided evidence that after human mesenchymal stem cells were treated with LL-37, human mesenchymal stem cells exhibited increased expression of let-7f and adhesion to athero-prone endothelium. This resulted in the induction of numerous beneficial bioactive factors, including cytokines and chemokines in an Apoe^{-/-} mouse model, these findings highlight the potential of stem cells in atherosclerosis treatment. A summary of the recent research progress on adult stem cell applications in frailty is presented in **Table 1**, and the main mechanisms of stem cells against frailty in different organs were also summarized in **Figure 1**.

Table 1. Stem cell applications in age-related diseases.

The types of stem cells	Application form	Frailty symptoms	Therapeutic effects	Potential mechanisms	References
hUCMSCs	hucMSCs derived exosomes	Parkinson's disease	Decrease the dopaminergic neuron of apoptosis; upregulated the dopamine levels, and dopamine metabolites	autophagy	[61]
monkey MSCs	iNSCs	Parkinson's disease	Give rise to dopaminergic neural cells	/	[62]
hAMSCs	GDNF transfected hAMSCs	Parkinson's disease	Promote the viability and therapeutic potential of hAMSCs in vivo	/	[63]
hNSCs	hNSCs derived exosomes	Alzheimer's disease	Decreased the expression of A β and p-tau, and decreased the neuronal inflammation	NF- κ B/ERK/JNK-related signaling pathways	[64]
MSCs	MSCs	Renal disease	Reduce renal tubular cell injury	TLR4-MyD88-NF- κ B Axis	[65]
AMSCs	AMSCs	Cardiac disease	Reduced aging associated cardiac damage	activates paracrine factors	[66]
BMMSCs	BMMSCs (TNF α -treated)	Atherosclerosis	Decreased suppressing inflammation, and immunosuppressive effect	/	[67]
Rabbit AMSCs	AMSCs	Atherosclerosis	Decreased the blood lipid levels, reduced accumulation of inflammatory macrophages	activating the STAT6 pathway	[68]
BMMSCs	bone marrow lineage-sca-1+ c-kit+ (LSK) cells	Cardiovascular disease	Induce senescence-like phenotypes	H3K27me3 demethylase-mediated epigenetic regulation	[69]
hBMMSCs	miR10a	Myocardial infarction	Promoted implanted stem cell survival and improved cardiac function	KLF4-BAX/BCL2 pathway	[70]

Table 1. (Continued).

The types of stem cells	Application form	Frailty symptoms	Therapeutic effects	Potential mechanisms	References
MSCs	MSCs derived exosomes	Stroke	Reduce myelin damage and enhances myelin maintenance	/	[71]
hBMMSCs	Circular RNAs	Osteoporosis	Suppressed osteogenesis and promoted adipogenesis	upregulates ROCK1	[72]
hUCMSCs	hucMSC-derived exosomes	Muscle atrophy	Increased grip strength, running endurance, and muscle mass	AMPK/ULK1-mediated autophagy	[73]
hUCMSCs	hUC-MSCs	Sarcopenia	Improved skeletal muscle strength, regulated expression of extracellular matrix protein, decreased cellular aging	autophagy	[74]
MSCs	magnetized MSCs	Sarcopenia	Decreased inflammation	increased IL6 and IL10 mRNA expression and decreased TNF- α and IL1 β mRNA expression	[75]
hUC-MSCs	hUC-MSCs	Chronic renal disease	Improve renal interstitial fibrosis; decrease renal cell apoptosis	/	[76]

Abbreviations:

hUCMSCs, human umbilical cord mesenchymal stem cells; iNSCs, induced neural stem cells; hAMSCs, human adipose derived mesenchymal stem cells; PD, Parkinson's disease; BMMSCs, bone marrow mesenchymal stem cells; NF- κ B, Nuclear factor kappa-B; KLF4, Kruppel like factor 4; ROCK1, Rho associated coiled-coil containing protein kinase 1; TAZ, transcriptional coactivator with PDZ-binding motif; TNF α , tumor necrosis factor α ; IL1 β , interleukin 1 β ; GDNF, glial-derived neurotrophic factor; MyD88, myeloid differentiation factor 88; PGC1 α , Peroxisome proliferator-activated receptor-gamma coactivator 1alpha; BAX, Bcl2 Associated X-protein; BCL2, B-cell lymphoma 2.

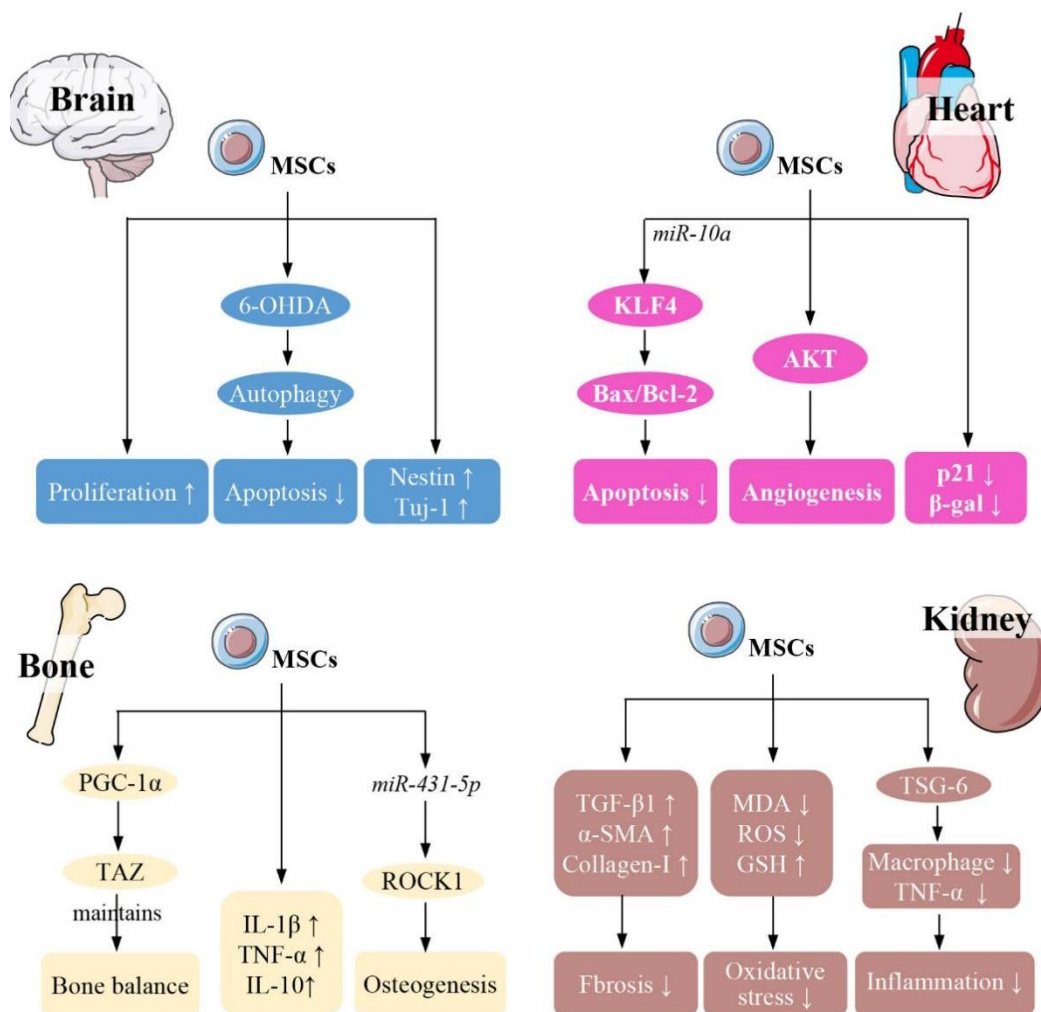


Figure 1. The main mechanisms of stem cells against frailty in different organs.

Abbreviations: MSCs, mesenchymal stem cells; 6-OHDA, 6-hydroxydopamine; KLF 4, Kruppel like factor 4; ROCK1, Rho associated coiled-coil containing protein kinase 1; TAZ, transcriptional coactivator with PDZ-binding motif; TNF- α , tumor necrosis factor α ; IL1 β , interleukin 1 β ; IL10, interleukin 10; TSG 6, Tumor necrosis factor-stimulated gene-6; TAZ, transcriptional coactivator with PDZ-binding motif; PGC1 α , Peroxisome proliferator-activated receptor-gamma coactivator 1alpha; BAX, Bcl2 Associated X-protein; BCL2, B-cell lymphoma 2; Tuj1, neuron-specific class III β -tubulin.

In addition to preclinical applications of stem cells for frailty, several clinical trials have been conducted to verify the efficacy and reliability of stem cells in frailty. For example, Golpanian et al. [77] conducted a non-randomized, dose-dependency clinical trials, including 15 patients by a single intravenous injection of three different concentrations of allogeneic MSCs (20-million, 100-million, or 200-million cells), long-term observation results demonstrated that allogeneic MSCs treatment for frailty patients was safe and effective [78]. Tompkins et al. [79] intravenously administered to the frail patients with 100 or 200-million allo-hMSCs to assess the safety and effectiveness of clinical application of allo-hMSCs. The results demonstrated that the allo-hMSCs exhibited superior therapeutic efficacy in frail patients, however, larger clinical trials are recommended to further evaluate the

safety and efficacy of allo-hMSC administration.

5. Application limitations of stem cell in the treatment of frailty

In recent years, the rapid development of stem cell technology has led to numerous reports on the beneficial therapeutic effects of stem cells in frailty, and several research teams have reported a clinical application of stem cells in the treatment of frailty. However, there are still several challenges that must be addressed before the application of stem cells in frailty can be fully realized. (1) The source of the stem cells. It has been reported that a variety of stem cells have been applied in the treatment of frailty, including hUCMSCs, iNSCs, iPSCs, and hAMSCs. However, due to the use of disparate stem cell types, culture media, and isolation techniques across different laboratories, the establishment of unified standards for stem cell sources may prove challenging. These factors could result in difficulty in establishing unified stem cells source standards may become an obstacle for stem cell clinical application in frailty. It is suggested that unified and standardized methods for stem cells isolation, cultivation, and differentiation and rigorous quality control is necessary; (2) The heterogeneity of MSCs. It has been proven that the MSCs or MSCs derivatives from different donors has cellular heterogeneity, a rigorous quality control of heterogeneity of MSCs is imperative prior to clinical application [80,81]; (3) Animal models of frailty. The development of new drugs is contingent upon the results of animal experiments, which in turn inform the design of subsequent clinical trials. The success or failure of drug development is therefore contingent upon the choice of an appropriate animal model; However, there is a paucity of literature reporting on the establishment of frailty models, frailty-related PD models and sarcopenia models. This represents a significant gap in our understanding of the pathogenesis of clinical patients, which presents a significant obstacle to the application of stem cells in frailty. The continuous research direction is the establishment of a standardized animal model that is as close as possible to human frailty. This is a priority area that requires urgent attention. (4) Policies and regulations of stem cell application. It is widely acknowledged that the policies and regulations governing the use of stem cells in a given country directly influence the potential applications and future research directions in this field. For instance, European and American countries have explicitly prohibited the conduct of ESC or iPSCs studies, which has directly resulted in the cessation of stem cell technology in those countries. It seems imperative that legislation be enacted governing the utilization, research, and application of stem cells at all levels.

6. Conclusion

In this review, we summarized the main risk factors for the occurrence and progression of frailty, the recent research progress preclinical and clinical applications of the stem cells in frailty and discussed cell applications in frailty and potential solutions to this issue. Frailty as a complex symptom caused by multiple risk factors, to develop optimal treatments, it is essential to conduct comprehensive research into the pathogenesis and etiology of frailty. This should include the

development of unified and standardized methods for stem cell cultivation, and differentiation, as well as rigorous quality control of MSC heterogeneity. Additionally, establishing standardized animal models and legislation governing stem cell research and applications are crucial steps for stem cell related drug development and preclinical and clinical applications. Once these challenges are addressed, the rapid advancement of precision medicine and regenerative medicine will greatly expand the potential and prospects of stem cell applications in frailty.

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