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REVIEW ARTICLE

Therapeutic potential of mesenchymal stem cells and their derivatives in sarcopenia

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Abstract

Sarcopenia is a common condition in the geriatric population. It refers to age-related and progressive decline in muscle mass and function, which has a great impact on one's mobility and quality of life. Patients with sarcopenia are mainly treated with nutritional therapy, exercise therapy, or a combination of both. Since the identification of mesenchymal stem cells (MSCs) several decades ago, many studies have explored the application of MSCs in the field of regenerative medicine. MSCs are popular candidates for cell-based therapy owing to their multipotent nature and immunomodulatory properties. Even though MSCs do not naturally differentiate into myogenic cells, they are important players in skeletal muscle health, as MSCs support myogenic differentiation of other cells and promote recovery of injured skeletal muscle. Recent studies have found that MSCs may be of benefits in the treatment of sarcopenia. This article gives an overview of sarcopenia and the role of MSCs in skeletal muscle homeostasis. It also discusses the therapeutic potential of MSCs and their derivatives, as well as the underlying mechanisms of the therapeutic effects of MSCs and MSC-based products in sarcopenia.

Keywords: Sarcopenia; mesenchymal stem cells; immunomodulatory effects; anti-apoptotic effects; cell-based therapy; mesenchymal stem cell derivatives

INTRODUCTION

Many changes in body composition take place with advancing age. One of these changes include a change in skeletal muscle mass, strength and quality.[1] These changes in skeletal muscle on the other hand, can critically impair physical performance, mobility, wellbeing and quality of life for the elderly. Skeletal muscles account for about 60% of the body's protein stores. Breakdown and synthesis of skeletal muscle proteins occur simultaneously and constantly in the body. A net negative protein balance and muscle wasting occur when there is a greater extent of skeletal muscle protein breakdown than synthesis. Research has found that an association exists between aging and skeletal muscle anabolic resistance. As the body ages, a decreased protein synthesis occurs in skeletal muscle in response to protein ingestion.[2] Besides, aging also blunts muscle protein synthesis in response to exercise.[3]

Sarcopenia refers to age-related and gradual decline in muscle mass and muscle function, which occurs commonly in the older adults. In 1989, Irwin Rosenberg was the first to propose the word "sarcopenia", which literally means "poverty of flesh" (sarx= flesh; penia= poverty in Greek).[4] Although it is mainly a disorder of the elderly, younger people with conditions such as malnutrition, disuse or cachexia can also have sarcopenia. Sarcopenia is of clinical significance because a declined skeletal muscle mass and muscle function is accompanied by increased frailty, risk of falls and mortality. In the past, research has shown that skeletal muscle mass is not only associated with mortality but is also a predictor of longevity in older adults.[5,6]

Mesenchymal stem cells (MSCs) are a

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type of adult stem cells that reside in multiple tissues in the body. Besides the bone marrow, other sources of MSCs include adipose tissue, muscle, amniotic fluid, endometrium, dental pulp, placenta, skin, synovium, synovial fluid, umbilical cord blood etc.[7] MSCs belong to a class of stem cells regarded as multipotent stem cells because of their ability to differentiate into multiple cell types that originate from the mesoderm (e.g. osteoblasts, chondrocytes, myocytes and adipocytes).[8] Besides, MSCs are also capable of transdifferentiating into cells of endodermal and ectodermal origins.[9] MSCs are popular therapeutic candidates because they can be easily cultured in the laboratory. The multipotent differentiation potential, immunomodulatory properties of MSCs, and the ability of MSCs to migrate and engraft in sites of injury, as well as their ability to secrete a vast array of soluble factors[10] add to their popularity among researchers and clinicians.

The treatment of sarcopenia involves several strategies, e.g. exercise therapy, nutritional intervention and drug intervention. Studies have shown that a combination of two or more approaches is better than a single approach. For instance, combined nutritional and exercise intervention is more effective than nutritional or exercise intervention alone.[11] On the other hand, MSCs offer an alternative therapeutic option in the treatment of sarcopenia in view of their regenerative and differentiation potentials, as well as other properties that may play a role in sarcopenia. This review gives an overview of sarcopenia and critically examines the current evidence on the therapeutic application of MSCs and their derivatives in sarcopenia intervention, with an emphasis on the underlying mechanisms of the therapeutic effects of MSCs and MSC-based products.

Sarcopenia

The European Working Group on Sarcopenia in Older People (EWGSOP) revised the operational definition of sarcopenia in 2018. Key criteria applied in the definition of sarcopenia include muscle strength, muscle quantity and quality, as well as physical performance. When a person has low muscle strength, he or she probably has sarcopenia and when low muscle quantity or quality is present, the diagnosis of sarcopenia is confirmed. Furthermore, sarcopenia is considered severe if these two criteria are accompanied by low physical performance.[12] As reported in a recent study, sarcopenia incurred a high economic burden, with an estimated total annual hospitalisation cost of USD$40.4 billion (or an average of USD$260 per person) in the United States.[13] On the other hand, an earlier study reported an estimated direct healthcare cost of USD $18.5 billion in the US in 2000 for sarcopenia.[14]

Although diminished muscle mass inevitably results in a loss in muscle strength, sarcopenia is not the same as dynapenia, which is defined as "the age-associated loss of muscle strength that is not caused by neurologic or muscular diseases".[15] Clark and Manini first introduced the term "dynapenia" in 2008 to emphasise the importance of loss of muscle strength and that it can be due to factors other than loss of muscle mass. Alternative mechanisms including changes in neurologic functions and contractile properties have been proposed for the underlying cause of dynapenia.[16] Research has shown that dynapenia is a more sensitive predictor of instrumental activities of daily living (IADL) and physical disability in basic activities of daily living (BADL) whereas sarcopenia is associated with loss of mobility in the elderly.[17] Another term "myopenia" is used to describe a rapid loss of muscle mass (i.e. $\geq$5% in 6 to 12 months) due to any illness regardless of age,[18] which is not to be confused with sarcopenia or dynapenia. This article focusses on sarcopenia and a discussion on dynapenia and myopenia is beyond the scope of this review.

Epidemiology

The peak muscle mass is achieved at around 30 years of age after which it gradually declines as one ages and accelerates from 50 years. By about 70 years, there is 20-40% decrease in muscle mass, which leads to sarcopenia.[19] Research has shown that loss of muscle mass and muscle strength occurs rapidly at advancing of age. A study demonstrated that for those aged 75 years, loss of muscle mass took place at rates of 0.64-0.70%/year and 0.80-0.98%/year for women and men respectively.[20] Greater rates were observed for loss of muscle strength at the same age, i.e. 3-4%/year and 2.5-3%/year for men and women respectively.[20]

Wide variations exist in the estimated prevalence of sarcopenia in different communities and clinical settings. An explanation for this observation is the application of different definitions, diagnostic criteria and tools in the diagnosis of sarcopenia. However, despite these differences, a considerable proportion of the

elderly population (even among healthy elderly people) has sarcopenia. In a systematic review consisting of 35 studies and 58,404 subjects, the global overall estimated prevalence of sarcopenia was 10%. The estimated prevalence was as high as 19% in men and 20% in women when Bioelectrical Impedance Analysis (BIA) was applied in muscle mass measurement.[21] Using the Asian Working Group for Sarcopenia (AWGS) criteria, Du *et al* noted a higher prevalence in males (19.2%) than females (8.6%) among subjects aged above 65 years. Sarcopenic obesity also showed a higher prevalence in males (7.0%) than females (2.4%) in the same study.[22] The estimated prevalence of sarcopenia and sarcopenic obesity using different methods is summarised in Figure 1.

Aetiology, risk factors and pathophysiology

There are two main categories of sarcopenia, i.e. primary and secondary sarcopenia. For the former, age is the most crucial factor whereas for the latter, factors other than age play a role in the development of sarcopenia. Some of the causes of secondary sarcopenia are related to one's activity level, nutrition status and the presence of certain diseases. In a study, unbalanced foods, prolonged sitting and insufficient activity increased the risk of sarcopenia in those >65 years in Taiwan but sleep duration was not associated with sarcopenia.[23] A higher body mass index (BMI) and smoking also increase the risk of sarcopenia.[24] Alcohol consumption is also linked to sarcopenia. In elderly women, sarcopenia prevalence was 2.8 times higher in binge drinkers than that of social drinkers.[25]

An increased prevalence of sarcopenia is observed in some medical conditions. For example, a study consisting of Asian subjects aged 60 years or above (1,537 individuals with diabetes mellitus and 5,485 individuals without diabetes mellitus) revealed a higher prevalence in those with diabetes mellitus (15.9% versus 10.8%).[26] Another study found that sarcopenia (but not handgrip strength) was associated with hypertension in the elderly.[27] Sarcopenia is also a common problem among patients with heart failure, with the condition more prevalent in hospitalised than ambulatory patients[28] while malnutrition and chronic inflammation have also been demonstrated to play a part in sarcopenia among elderly with hip fractures.[29]

The underlying causes and pathophysiology of age-related muscle atrophy are complex, which involve an interplay of local, systemic and risk factors (refer to Figure 2). Locally, several changes in muscle composition occur with advancing age, which may include a redistribution of muscle types[30] and infiltration by adipocytes,[31] contributing to sarcopenic obesity. Aging is also accompanied by a change in protein metabolism such as protein modifications and a shift towards protein breakdown,[32] as well as an increased susceptibility to oxidative stress[33] and impairment in mitochondrial function.[34] In addition, the number of satellite cells in skeletal muscle decreases with advancing age,[35] which leads to decreased regenerative capacity.

Systematically, aging is associated with a decline in anabolic hormones, increased inflammation (known as inflammaging)[36] and immune dysfunction (known as

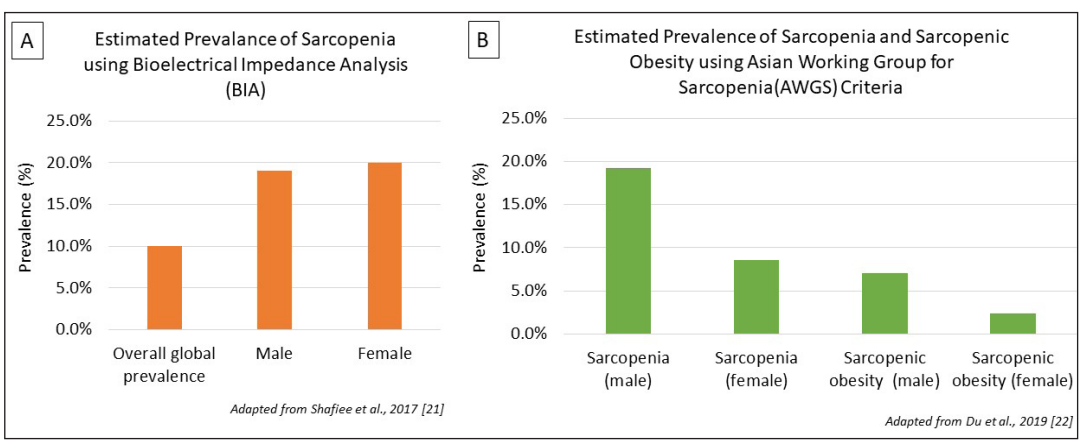

FIG. 1: Estimated prevalence of sarcopenia and sarcopenic obesity using different methods.
(A) Estimated prevalence of sarcopenia using Bioelectrical Impedance Analysis (BIA). (B) Estimated prevalence of sarcopenia and sarcopenic obesity among subjects aged >65 years using Asian Working Group for Sarcopenia (AWGS) criteria.

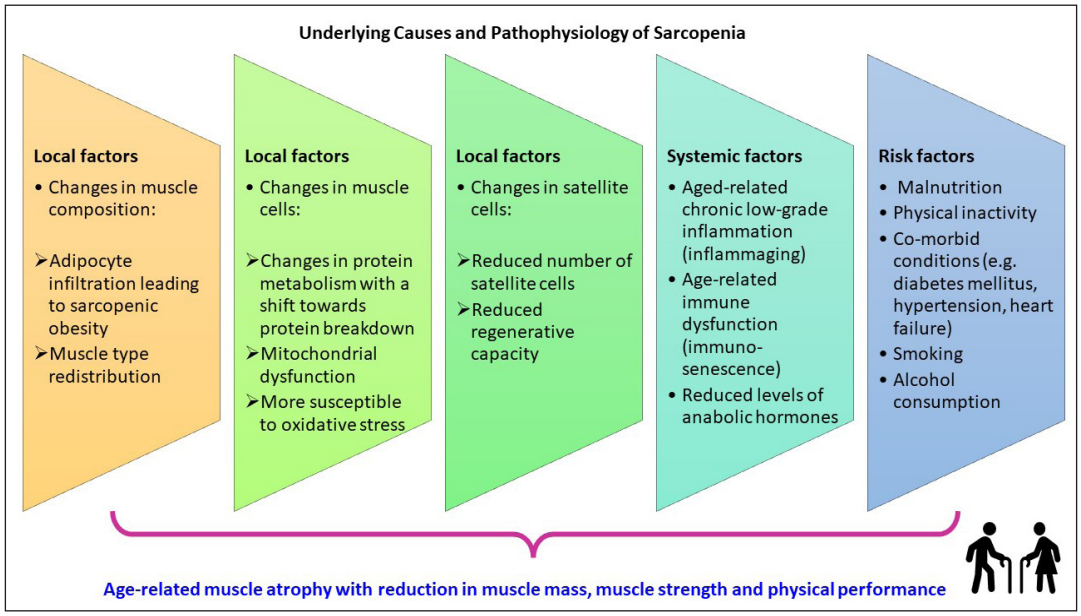

FIG. 2: Underlying causes and pathophysiology of sarcopenia.

immunosenescence).[37] In inflammaging, there is an increased level of serum inflammatory markers resulting in chronic low-grade inflammation.[36] Together, in the presence of risk factors such as malnutrition, physical inactivity and co-morbid conditions, these aetiopathological factors contribute to a reduction in muscle mass, muscle strength and physical performance. MSCs are potential therapeutic candidates for sarcopenia because some properties of MSCs such as their immunomodulatory and immunosuppressive nature, [38] as well as MSCs' ability to interact with satellite cells in skeletal muscle[39] may target some of the pathophysiologic processes in sarcopenia.

Diagnosis

Several international initiatives have set the diagnostic criteria for sarcopenia. These include the AWGS, EWGSOP2, Sarcopenia Definition and Outcomes Consortium (SDOC) criteria. The parameters used in these diagnostic criteria include muscle strength, muscle mass, physical performance and gait analysis,[11,12,40] which are summarised in Table 1.

Treatment

Nutritional therapy, exercise therapy or a combination of both are therapeutic approaches commonly used in the treatment of sarcopenia. Malnutrition, sarcopenia, cachexia and frailty often co-exist in the elderly population.[41] Physiological anorexia and decreased protein/energy are factors contributing to age-related sarcopenia. A balanced diet is important in maintaining muscle mass and muscle function whereas research has shown a significantly lower consumption of certain macronutrients (e.g. lipids and proteins) and micronutrients (e.g. iron, phosphorus, magnesium, potassium and vitamin K) in patients with sarcopenia when compared to subjects without sarcopenia.[42]

Research has found that the effects of combined exercise therapy and nutritional therapy are better than the effects of either therapy alone. The International Clinical Practice Guidelines for Sarcopenia (ICFSR) recommend resistance-based exercise, together with protein supplementation or a diet rich in proteins as treatment strategies for sarcopenia. However, the ICFSR did not give any recommendation for the use of anabolic hormones or vitamin D supplementation.[43]

In some cases, aggressive nutritional therapy (ANT) may be used for the treatment of sarcopenia. The target energy for ANT includes the sum of total energy expenditure (TEE) plus energy accumulated. For example, to gain 1 kg of lean mass, an accumulated energy of 7500 kcal is needed (for people aged 10-40 years). Therefore, if one needs to gain 1 kg over a period of 30 days, the target daily energy requirement is TEE +250 kcal per day. Usually, it is recommended that ANT be combined with aggressive rehabilitation.[44]

Table 1 Criteria used in sarcopenia diagnosis

Criteria	Low/ reduced muscle strength		Low muscle mass			Physical performance	Low usual gait speed
AWGS	By handgrip < 28 kg (men) < 18 kg (women)		ASM/Height^2 Less than 7.0 kg/m^2 (men) Less than 5.4 kg/m^2 by DXA (women) Less than 5.7 kg/m^2 by BIA (women)			Any criterion below: 6-meter walk < 1.0 m/s 5-time chair stand test ≥ 12s SPPB ≤ 9	
EWGSOP2	By handgrip < 27 kg (men) <16 kg (women)	By chair stand test >15s for 5 rises	ASM/Height^2 < 7.0 kg/m^2 (men) <5.5. kg/m^2 (women)	or or	ASM < 20 kg (men) < 15 kg (women)	Any criterion below: Gait speed: ≤ 0.8 m/s SPPB: ≤ 8 point score TUG: ≥ 20s 400m walk test: ≥ 6 min /NC	
SDOC	By handgrip <35.5 kg (men) <20 kg (women)						Slowness: <0.8 m/s

Note: 1) For AWGS, diagnosis=low muscle mass + reduced muscle strength. Severity= low muscle mass + reduced muscle strength + any criterion for physical performance. 2) For EWGSOPS2, diagnosis=low muscle strength + low muscle mass. Severity= Presence of any criterion for physical performance.3) For SDOC, diagnosis=low muscle strength + low usual gait speed. Abbreviations: ASM= appendicular muscle mass; AWGS= Asian Working Group for Sarcopenia; BIA= bioelectrical impedance analysis; EWGSOP2= European Working Group on Older People 2; NC= non-completion; SDOC= Sarcopenia Definition & Outcome Consortium; SPPB=short physical performance battery; TUG=timed-up and go test

Several pharmacological agents have been used in the treatment of sarcopenia. However, there is no Food and Drug Administration (FDA)-approved drug specifically indicated for sarcopenia. Some pharmacological agents that may be beneficial in sarcopenia include (1) myostatin inhibitors, which may help in enhancing lean muscle mass; (2) testosterone, which have been shown to increase muscle mass, muscle strength and improve physical performance, as well as decrease fat mass; (3) growth hormone, which may be beneficial in increasing lean tissue mass and decreasing fat mass and (4) angiotensin-converting enzyme (ACE) inhibitors, with some evidence for improved exercise capacity. However, the use of these pharmacological agents may be accompanied by side effects. For example, the use of testosterone may increase risks of cardiovascular disease and worsen benign prostatic hyperplasia while the use of growth hormone may induce fluid retention and orthostatic hypotension etc. (reviewed by Lo *et al*).[45]

Regenerative medicine and mesenchymal stem/ stromal cells

Regenerative medicine is an evolving and innovative field of medicine concerned with the regrowth, regeneration, replacement or repair of damaged cells, tissues or organs. The application of therapeutic stem cells and tissue engineering, as well as the production of artificial organs for therapeutic intervention are under the umbrella of regenerative medicine.[46] The discovery of MSCs in the 1970s has revolutionised the field of regeneration medicine. With advancing technologies in molecular biology, as well as enhanced techniques in transplantation, MSCs have been extensively investigated and applied in various conditions owing to several favourable properties MSCs possess.

Like any other types of stem cells, MSCs possess the ability to self-renew and differentiate into more specialised cell types. However, to define a cell as MSC, it must exhibit several properties in addition to the general properties of a stem cell. According to the International Society for Cell and Gene Therapy (ISCT) guidelines published in 2006, a cell needs to fulfil some minimum criteria before it can be considered an MSC, which include adherence to tissue culture plastic, the presence and absence of certain surface antigen markers and the ability to differentiate to chondroblasts, osteoblasts and adipocytes.[47] The ISCT later published a position statement on mesenchymal stromal cells in 2019 and the Mesenchymal Stromal Cell committee continued to support the use of the acronym "MSCs" with three recommendations.[48] The ISCT criteria for the characterisation of MSC are summarised in Figure 3.

The rich source of MSCs make them an ideal cell type for regenerative medicine. MSCs are multipotent stem cells located in many tissues. MSCs can be isolated from sites such as the

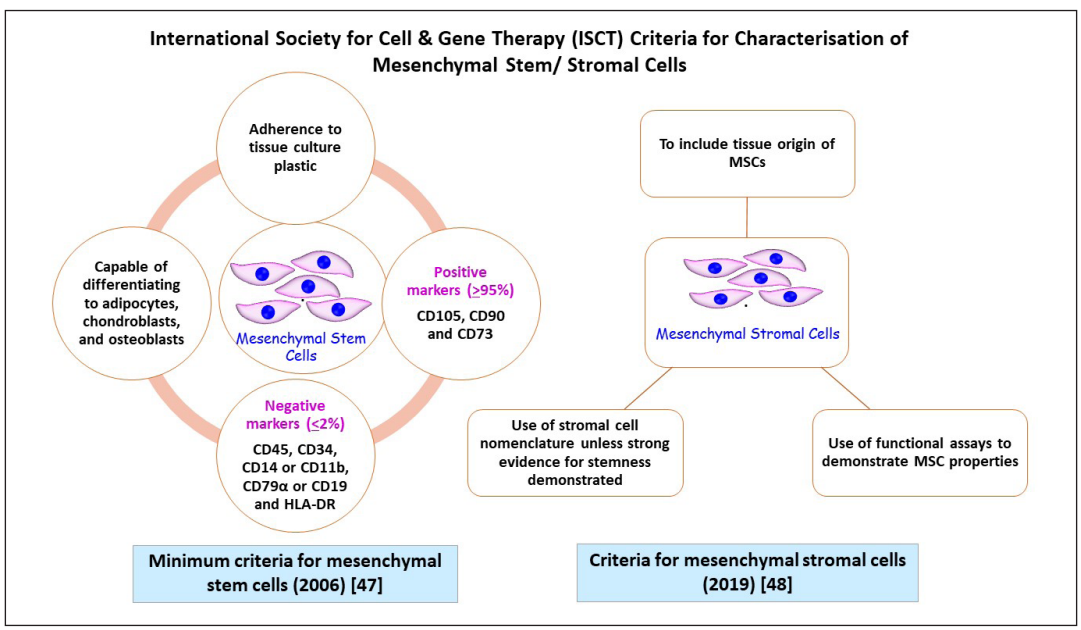

FIG. 3: ISCT criteria for characterization of mesenchymal stem/ stromal cells published in 2006 and 2019.

bone marrow, placenta, amniotic fluid, adipose tissue, dental tissue, umbilical cord blood etc.[49] Research has shown that MSCs are capable of differentiating into cells of mesodermal origin (e.g. adipocytes, chondrocytes and osteoblasts). MSCs can also transdifferentiate into cells of endodermal (e.g. hepatocytes, pancreatic β cells etc.) and ectodermal (e.g. neurons) lineages (reviewed by Andrzejewska *et al*).[50]

MSCs are very popular among researchers and scientists because they possess several properties that make them promising candidates in cell-based therapy. When compared to other stem cell types like embryonic stem cells (ESCs), isolation and culture of MSCs in the laboratory are relatively easy. The immunosuppressive properties of MSCs allow the use of both allograft and autograft.[51] MSCs can suppress proliferation and activation of different cells of the innate and adaptive immune system. The immunosuppressive effects of MSCs are mediated either via direct contact with the immune cells or via paracrine effects of secreted soluble factors.[52] The immunosuppressive nature of MSCs allows these cells to be transplanted without rejection and the need of immunosuppressants. Another favourable property of MSCs is their homing ability,[53] which allows MSCs to adhere and engraft in injured or inflamed sites, enhancing tissue repair and regeneration. Besides, MSCs are also free from the ethical issues concerning ESCs, and have a lower risk of developing into teratomas.[51]

However, one set back in using MSCs is their limited replicative lifespan. As a result, alteration of the various functions of MSC including their multipotency may arise after many passages.[51] The heterogeneity of MSCs is another limitation for using MSCs, which makes it challenging to derive consistent conclusions regarding the potential therapeutic effects of MSCs. Other challenges concerning the use of MSCs include short cell survival and no remarkable improvements after transplantation in some cases, as well as a lack of consistent data on the optimal doses and route of MSC administration.[54] In addition, there exists wide gaps in the regulation of MSC therapy by authorities in different countries. Worldwide, there are at least ten approved therapies involving MSCs for various conditions. However, the FDA has not approved any one of these MSCs products to be used in the United States (reviewed by Wright *et al*).[55]

Role of satellite cells and MSCs in skeletal muscle homeostasis

Skeletal muscle's regenerative potential acts as a compensatory mechanism in conditions with muscle loss. However, the ability to regenerate may not be sufficient to support long-term skeletal muscle regeneration especially in chronic conditions. The regeneration of muscle fibres depends on satellite cells (SCs), which are a kind of muscle stem cells.[56] SCs were first discovered by Mauro in 1961[57] and were considered as a new source of myonuclei in skeletal muscle tissue after birth.[58] The progeny of SCs are the myoblasts, which have the ability to form new myofibres by fusing with one another, to fuse with existing muscle fibres, or to self-renew and replenish the resident pool of SCs.[59]

Differing views exist in the published literature concerning the role of SC depletion in sarcopenia. In a study, Fry *et al* induced SC depletion in male sedentary mice. Muscle analysis at various time intervals during aging showed normal-size muscle with a reduced regenerative capacity. However, an increase in fibrosis and change in fibre type composition were not observed during aging. These findings imply that sarcopenia was not worsened by a lifelong depletion of SCs and that muscle loss may be attributed to other factors such as muscle fibrosis related to aging.[60] On the contrary, Englund *et al* observed that balance and coordination, muscle proprioceptor size and overall running volume were reduced in SC-depleted mice. In response to lifelong physical activities, SC involvement was needed for optimal muscle fibre hypertrophy and that SCs contribute to physical function preservation in aging, as well as muscle adaption in sustained physical activity.[61]

Although MSCs do not naturally differentiate into myogenic cells, they play a crucial role in muscle homeostasis. MSCs do so by interacting with SCs and other cell types in skeletal muscle. One type of tissue-specific MSCs that interact with SCs are known as fibro-adipogenic progenitors (FAPs),[39] which help in maintaining skeletal muscle health. FAPs have the ability to differentiate into fibrogenic- and adipogenic- but not myogenic cells. Earlier research has shown that FAPs remain quiescent in healthy muscle, but proliferate in injured muscle and play a supportive role in myogenesis.[61] FAP depletion in mice, on the other hand, resulted in muscle mass reduction, decreased myofibre size,[63] decreased muscle force, muscle atrophy and a reduction in muscle stem cell number.[64,65] On the other hand,

senescent mesenchymal progenitor cells (MPCs) in the skeletal muscle of aged rats have been found to hasten sarcopenia through inhibition of myoblast fusion.[66]

Applications of MSCs and their derivatives in sarcopenia

In recent years, researchers have explored the therapeutic potentials of MSCs in sarcopenia. This section discusses the potential use of MSCs and their derivatives in the treatment of sarcopenia and the underlying mechanisms involved in the therapeutic effects of MSCs and MSC-based products in sarcopenia.

In vitro and animal studies

Exosomes are extracellular vesicles (EVs) secreted by many eukaryotic cells, which include MSCs. Lately exosomes have gained much popularity and attention due to the vast array of substances (e.g. proteins, DNA, RNA, lipids and glycoconjugates) they contain.[67] In a study, BMSC-derived exosomes (Exos) have been shown to inhibit muscle atrophy *in vitro and in vivo*. Li *et al* reported that C2C12 myotubes (a skeletal muscle cell line) exhibited a decrease in diameter when treated with dexamethasone (DEXA) and the reduction in diameter was inhibited when C2C12 myotubes were co-cultured with MSC-Exos. Upregulation of miR-486-5p (a microRNA that improves muscle function and strength when over-expressed) and downregulation of FoxO1 (a transcription factor that plays a role in muscle atrophy) played a part in the underlying mechanisms in the MSC-Exos intervention. DEXA-induced muscle atrophy was also inhibited *in vivo* when mice were treated with MSC-Exos. miR-485-5p inhibitor, on the other hand, was shown to reverse such inhibition both *in vitro* and *in vivo*. The study concluded that MSC-Exos exhibited inhibitory effects on DEXA-induced muscle atrophy via the miR486-5p/FoxO1 axis.[68]

Kono *et al* investigated the effects of magnetised C57BL/6 mouse MSCs *in vitro* and *in vivo*. When magnetised MSCs were co-cultured with liposome (LPS)-stimulated C2C12, there was an increase in interleukin (IL)-6 and inducible nitric oxide synthase (iNOS) mRNA expression and a decrease in tumour necrosis factor-alpha (TNF-α) and IL-1β mRNA expression in C2C12. MSC retention in inflamed skeletal muscle of mice was enhanced following magnetisation whereas IL-6 and IL-10 mRNA expression was increased and that of Il-1β and TNF-α was decreased in inflamed skeletal muscle of mice.[69]

Takegaki *et al* injected C57BL/6 mouse bone marrow-derived mesenchymal stem cells (BMSCs) in the gastrocnemius muscle of mice and observed upregulation of genes related to muscle SCs, mechanistic target of rapamycin complex 1 (mTORC1) signaling activation, increased protein synthesis, as well as enhanced protein ubiquitination and autophagosome formation. Past research has indicated that mTORC1 may play a part in protein synthesis and muscle hypertrophy whereas protein ubiquitination and autophagosome formation are associated with muscle protein degradation. Findings of the study, therefore, imply that intramuscular injection of MSCs plays a part in activation of anabolic and catabolic systems associated with an increased muscle protein turnover.[70]

Uezumi *et al* reported that the mesenchymal-specific gene *Bmp3b* played a role in skeletal muscle health maintenance in a mouse model. In young muscle, there was an abundant expression of *Bmp3b* in mesenchymal progenitors (MPs). However, *Bmp3b* expression declined significantly with aging. Mice depleted of MPs showed features that were similar to those of sarcopenia (e.g. atrophied myofiber, muscle weakness, fibre type changes and neuromuscular junction denervation). However, when recombinant *Bmp3b* was administered to aged mice, a reversal of sarcopenic phenotypes was observed, suggesting the importance of MPs in muscle integrity maintenance, as well as the effects of MP age-related changes in sarcopenia development.[65]

When compared to control mice, Kurosawa *et al* demonstrated that transgenic mice with forced *Bmp3b* expression had a heavier muscle mass, a decreasing fibrosis trend and preservation of neuromuscular junction innervation. These findings suggest that the mesenchymal-specific *Bmp3b* gene attenuates deterioration of aging muscles.[71] Therefore, therapies that target the preservation of the juvenescence of MPs may be beneficial in sarcopenia.

Wang *el al* administered human Wharton's Jelly derived (hWJ)-MSCs in aged C57BL/6J mice induced with sarcopenia and reported enhancement in muscle strength and endurance of the whole body, increased muscle mass of gastrocnemius and increased cross-sectional area (CSA) of the myofibres. There was also a reduction in myonucleus apoptosis. IL-6

and TNF-α (proinflammatory cytokines) were downregulated while IL-4 and IL-10 (anti-inflammatory cytokines) were upregulated. An increased SC proliferation was observed as indicated by an increase in BrdU and paired box 7 (Pax-7) expression. The study concluded that hWJ-MSCs may be beneficial in sarcopenia in aged mice and the likely underlying mechanisms include SC activation, decreased apoptosis and the anti-inflammatory effects of hWJ-MSCs.[72]

Shehata *et al* demonstrated the effects of BM-MSCs in rats with induced skeletal muscle chemodenervation atrophy. Rats were divided into 1) induced-atrophy group, 2) BM-MSC treatment group and 3) recovery group. Improved histological structure was observed in skeletal muscle of rats treated with BM-MSCs. In the muscle fibre cytoplasm, there was a strong positive immunochistochemical reaction for the apoptotic Bax protein for the induced-atrophy group when compared to the weak positive reaction for the treatment group, whereas the recovery group exhibited a moderate positive reaction. These findings suggest anti-apoptotic effects of the BM-MSCs in induced muscle atrophy.[73]

Li *et al* injected rat bone marrow-derived (BM)-MSCs and phosphate-buffered saline (PBS) in rats with immobilisation-induced muscle atrophy. Differences in cross-sectional area of myofibres, muscle mass or peak tetanic forces between rats treated with BM-MSCs and PBS were not significant. However, rats treated with BM-MSCs demonstrated a significantly greater SC proliferation ($p<0.05$) and significantly reduced mynonuclear apoptosis. The study also reported Bax (a pro-apoptotic gene) downregulation as well as Bcl-2 and p-Akt (anti-apoptotic genes). The findings indicate that the beneficial effects of BM-MSCs in muscle atrophy could be due to SC activation and inhibition of myonuclear apoptosis.[74]

Clinical studies

Clinical studies on direct therapeutic benefits of MSCs in sarcopenia are scarce in the published literature. However, several clinical studies have explored the effects of MSCs in frail individuals and demonstrated improved physical functions related to skeletal muscle health. Sarcopenia can be considered as a physical manifestation of frailty and both conditions share a common set of impairment in physical functions i.e. slow gait speed, weak muscle strength and poor balance.[75] The benefits of MSCs in sarcopenia may be inferred from improvements in physical functions observed in frail individuals treated with MSCs, which provide new insights into MSC therapy in sarcopenia management.

In a Phase I clinical study, Golpanian *et al* administered allogenic human MSCs (allo-hMSCs) intravenously (IV) in 15 aging frail individuals with a mean age of 78.4 years (+/-4.7 years). At 3 and 6 months, there was a significant increase in 6-minute walk distance with a significant reduction in TNF-α. An improvement of the physical component of the SF-36 quality of life assessment was also reported. IV infusions of allo-hMSCs were well tolerated in the subjects, with no reported serious adverse events related to treatment. These findings suggest that MSCs may enhance the physical functions and immunologic status of aging frail individuals.[76] Hence, the potential therapeutic benefits of MSCs in sarcopenia should be explored in future studies, as both conditions are inter-related.

Tompkins *et al* reported similar findings using allo-hMSCs in individuals with aging frailty in a Phase II clinical study. Thirty subjects with a mean age of 75.5 years (+/-7.3 years) were given IV allo-hMSCs and demonstrated significant improvement in short physical performance exam, 6-minute walk test and forced expiratory volume in one second (FEV1) when compared to the control groups. Serum TNF-α and B cell intracellular TNF-α decreased significantly in patients receiving allo-hMSCs when compared with those in the placebo groups. A reduction in early and late activated T cells was also observed. Allo-hMSCs were well tolerated in the subjects with no reported severe adverse effects.[77] These findings are in tandem with those reported by Golpanian *et al*,[76] suggesting the feasibility of using MSCs to improve physical functions and chronic inflammation associated with aging. The applications of MSCs and MSC derivatives in sarcopenia are summarised in Table 2.

It is worth mentioning that although frailty and sarcopenia are defined differently, research has shown that these the two conditions are significantly associated, and that there is remarkable overlap concerning parameters of physical function impairment such as slow gait speed and poor grip strength etc. On the other hand, frail individuals are more likely to develop sarcopenia.[78] In addition, both frailty and sarcopenia share some similarities in pathophysiology, owing to age-related changes in the immune system such as immunosenescence

Table 2: Summary of applications of MSCs in sarcopenia

Type of MSCs	Key findings	Mechanism	Reference
***In vitro* studies**			
BMSC-derived exosomes/	Inhibition of reduction in C2C12 myotubes diameter induced by dexamethasone	Upregulation of miR-486-5p Downregulation of FoxO1	[68]
Magnetized C57BL/6 mouse MSCs/	Immunomodulatory effects in C2C12 myotubes	Increase in the mRNA expression of IL-6 and iNOS Decrease in IL-1β and TNF-α mRNA expression	[69]
Type of MSCs	**Key findings**	**Mechanism**	**References**
***In vivo* studies**			
BMSC-derived exosomes/	Inhibition of dexamethasone-induced skeletal muscle atrophy in mice	Upregulation of miR-486-5p Downregulation of FoxO1	[68]
Magnetised C57BL/6 mouse MSCs/	Enhanced magnetized MSC retention in inflamed skeletal muscle of mice Immunomodulatory effects of MSCs in inflamed skeletal muscle of mice	Increase in the mRNA expression of IL-6 and iNOS Decrease in IL-1β and TNF-α mRNA expression	[69]
C57BL/6 mouse BMSCs	Increased anabolic and catabolic processes and increased protein turnover in mice injected with MSCs in gastrocnemius muscle	mTORC1 signalling activation Enhanced protein ubiquitination and autophagosome formation.	[70]
Mesenchymal progenitors (MPs)	Depletion of MPs showed features similar to those of sarcopenia (e.g. atrophied myofiber, muscle weakness, fibre type changes and neuromuscular junction denervation) Reversal of sarcopenic phenotypes following recombinant *Bmp3b* administration in aged mice	Effects mediated via mesenchymal-specific gene *Bmp3b*	[65]
Mesenchymal progenitors	Transgenic mice with forced *Bmp3b* expression showed a heavier muscle mass, a decreasing fibrosis trend and preservation of neuromuscular junction innervation	Effects mediated via mesenchymal-specific gene *Bmp3b*	[71]
hWJ-MSCs	Enhancement in muscle strength and endurance of the whole body, increased muscle mass of gastrocnemius and increased cross-sectional area of the myofibres Increased satellite cell proliferation Reduction in myonucleus apoptosis Reduction in TNF-α, and IL-6 Upregulation of IL-6 and IL-10	SC activation Anti-apoptotic effects Anti-inflammatory or immunomodulatory effects	[72]

BM-MSCs	Improved histological structure in mice treated with BM-MSCs after induced atrophy Rats treated with BM-MSCs exhibited only weak immunohistochemical reaction for the apoptotic protein (Bax) while untreated mice with induced atrophy showed a strong positive reaction for Bax.	Suggestive of anti-apoptotic effects of BM-MSCs	[73]
Rat BM-MSCs	Increased SC proliferation Reduced mynonuclear apoptosis Bax (pro-apoptotic) downregulation Bcl-2 and p-Akt (anti-apoptotic) upregulation	SC activation Anti-apoptotic effects	[74]
Type of MSCs	**Key findings**	**Mechanism**	**References**
Clinical studies			
Allo-hMSCs/	Phase I clinical study IV allo-MSCs in frail individuals Increase in 6-minute walk distance Reduction in TNF-α. Improvement of the physical component of the SF-36 quality of life assessment	Suggestive of anti-inflammatory or immunomodulatory effects in frail individuals	[76]
Allo-hMSCs/	Phase II clinical study IV allo-hMSCs in frail individuals Improvement in short physical performance exam, 6-minute walk test and FEV1 Reduction in serum TNF-α and B cell intracellular TNF-α. Reduction in early and late activated T cells	Suggestive of anti-inflammatory or immunomodulatory effects in frail individuals	[77]

and inflammaging.[79] Therefore, data gathered from the application of MSCs in frail individuals provides insight into the potential use of MSCs in sarcopenia, which warrants future exploration.

CONCLUSIONS

In older adults and frail individuals, sarcopenia is a common condition that has a great impact on one's physical activity and wellbeing. Differences in the prevalence of sarcopenia exist in the published literature owing to the use of different diagnostic criteria and tools. Traditionally, treatment of sarcopenia involves nutritional therapy, exercise therapy or a combination of both. Research has shown that some pharmacological agents have beneficial effects in sarcopenia. However, there is no drug approved specifically for the treatment of sarcopenia. On the other hand, researchers have explored the use of MSCs and their derivatives in sarcopenia in recent years. Although MSCs do not naturally differentiate into myogenic cells, by interacting with SCs and immune cells, MSCs contribute to skeletal muscle homeostasis.

In recent years, it has become increasingly obvious that MSCs may be potential therapeutic candidates in sarcopenia. Numerous *in vitro* as well as animal studies have shown the beneficial effects of MSCs and their derivatives. Some underlying mechanisms of the therapeutic effects of MSCs and their derivatives include anti-inflammatory-, immunomodulatory- and anti-apoptotic effects on muscle atrophy. MSCs have also been shown to activate SCs in animal models with induced skeletal muscle atrophy using various methods.

Comparatively, there are few clinical studies on the application of MSCs in sarcopenia. Much of what we know about MSCs' effects on skeletal muscle health comes from administration of MSCs in aging and frail individuals. Although sarcopenia and frailty are two closely related conditions, direct evidences are needed to support the clinical use of MSCs for sarcopenia. Since many clinical studies have been carried out on MSCs in other conditions and an excellent safety profile has been established for MSCs in clinical use, there is a need for clinical trials to explore and evaluate the efficacy of MSCs alone or in combination with other therapeutic approaches for the management of sarcopenia in the elderly.

Future clinical studies should involve sarcopenic patients using established diagnostic criteria rather than patients with frailty, with a good sample size. These studies should also explore the underlying mechanisms of action for the beneficial effects of MSCs or MSC-based products in sarcopenia. In addition, due to the heterogeneity of MSCs, future research should examine whether MSCs from different sources will yield different clinical outcomes and identify the type of MSCs that are suitable for use in the treatment of sarcopenia. A promising source could be induced pluripotent stem cells-derived MSCs, where a more homogenous type of MSCs could be generated. The optimal route of MSC administration may also be an area of interest for future research.

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