Mesenchymal Stem Cells and Inflammaging

Subjects: Cell Biology

Contributor: Jia Xian Law

Rapid growth of the geriatric population has been made possible with advancements in pharmaceutical and health sciences. Hence, age-associated diseases are becoming more common. Aging encompasses deterioration of the immune system, known as immunosenescence. Dysregulation of the immune cell production, differentiation, and functioning lead to a chronic subclinical inflammatory state termed inflammaging. The hallmarks of the aging immune system are decreased naïve cells, increased memory cells, and increased serum levels of pro-inflammatory cytokines. Mesenchymal stem cell (MSC) transplantation is a promising solution to halt immunosenescence as the cells have excellent immunomodulatory functions and low immunogenicity.

mesenchymal stem cells aging inflammaging frailty immune system

1. Introduction

Frailty can be defined as a decline in physiological reserve across organ systems; it afflicts geriatric subjects above the age of 65. Immunosenescence is the term used to refer to profound changes in the immune system related to age. Immunosenescence involves dysregulation of the immune functions at both cellular and serological levels [1]. As a result of degenerating immunity, older age groups are more susceptible to severe infections with poor prognoses [2]. The risk of contracting community-acquired pneumonia increased by 21% in older adults of 65–74 years compared to younger patients, with an even higher incidence in older adults 85 years and above [3][4]. Bacteremia and sepsis are also more prevalent among older adults. More troubling—older adults have a higher risk of morbidity and developing cognitive decline post-infection [5][6]. Interestingly, older adults have higher autoimmunity, but not autoimmune disorders. The autoimmunity in older adults is associated with the high levels of circulating T-regulatory cells (Treg) and reduced CD4/CD8 ratio. Subsequently, this predisposes the aging host to infection and cancer [7]. The increasing age also hampers the effects of vaccination unless the vaccine is developed to bypass this concern, i.e., conjugating it with an adjuvant. Hence, immunization for the aging population is limited [1][8][9][10].

As a direct result of senescence, the immune system is in a constant subclinical inflammatory state known as ‘inflammaging’. Inflammaging is conjectured to be a consequence of activation of innate immunity and declination of adaptive immunity without exogenous stimuli. This state is associated with the cytokine’s milieu that skews towards a pro-inflammatory phenotype. The exact relationship between inflammaging and the disease state is yet to be elucidated [11]. However, most age-related degenerative diseases share similar inflammatory pathogenesis to which inflammaging may further exacerbate the disease process and its morbidity. The common inflammatory disease includes cardiovascular disease (myocardial infarction, hypertension, atherosclerosis), cognitive

impairments (Alzheimer's disease, Parkinson's disease), rheumatoid arthritis, and metabolic diseases (type II diabetes) [11][12][13].

The population aging is rapidly accelerating. The United Nations speculates that the number of people aged 65 years old and older will double between 2019 and 2050. In 30 years, one out of six people worldwide will be categorized in the "older adult" age bracket [14]. The older adult population is accompanied by a state of physiological vulnerability and declining ability to maintain homeostasis and respond to stress. This clinical expression of age-related decline is also known as frailty. Frailty and inflammation are strongly correlated where the serum levels of inflammatory markers are significantly higher in the older age group compared to the younger age group [15]. Frailty includes functional and structural alterations in multiple organ systems and impaired immune responses, which predispose to a plethora of disorders [16][17]. Consequently, the older adult population is a significant financial burden to the healthcare system [18]. Although the presentation of diseases may be incited by other risk factors, aging is a significant contributing mechanism due to the inevitable frailty development.

Currently, there are a few measures that may delay frailty onset and improve the morbidity of age-associated disease. The management of geriatric patients includes implementing calorie restriction, exercise regimes, and hormonal supplementations [12][19][20]. Diets high in n-3 polyunsaturated fatty acids and vitamin D have positive outcomes in reducing circulating levels of inflammatory molecules, namely C-reactive protein (CRP) and interleukin (IL)-6, as well as lower the mortality of the inflammatory diseases [21][22]. Zhang et al. showed that physical exercise can delay cognitive impairment while Ng et al. reported that cognitive training can improve physical mobility and strength [23][24]. The studies also showed that a mix of interventions (exercise and/or nutrition and/or cognitive training) would have better results than just either one [25]. Frailty is a complex condition that is unique to every individual; these clinical treatments require personalization to directly intercept immunological frailty. Moreover, Zhang et al. have found that the frailty index scoring system does not necessarily reflect the conditions the subject is facing. Some elderly may still be classified as pre-frail due to the cut-off score, but were experiencing frailty in different domains, be it cognitive or functional [23]. In the systemic review composed by Apostolo et al., the current personalized approach to manage disease-associated frailty has failed to produce consistent results [25]. Hence, there is yet an exact solution to frailty.

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that can be isolated from the bone marrow, adipose tissue, dental tissues, skin, salivary gland, limb buds, menstrual blood, and perinatal tissues [26][27][28][29]. MSCs can differentiate into adipocytes, osteoblasts, and chondrocytes. Although MSCs do not differentiate into immune cells, MSCs provide a supporting microenvironmental niche for hematopoietic stem cells (HSCs) to differentiate into myeloid and lymphoid cells, which are essentially the immune cells. This specialized environment plays an important role to maintain the longevity of HSCs by controlling their proliferation and apoptotic activities [30].

One of the speculated theories of declining immunity as the host ages is the MSC senescence. Subsequently, the functions and structures of MSCs, which are significant in maintaining the immune system, diminishes [31]. Although they are multipotent, mesenchymal progenitors exist in a small population, only consisting of 0.001% to

0.01% bone marrow mononuclear cells. Therefore, ex vivo expansion of MSCs and subsequent administration of optimized dosage is necessary to maintain and boost the effects of MSCs in vivo [32]. Furthermore, numerous in vivo and in vitro studies have proven that MSCs have low immunogenicity, excellent immunomodulatory function, and homing capability to regenerate damaged tissues through multipotent differentiation and paracrine secretion [11][33][34][35][36]. Despite that, the current studies are not primarily focused on aging or the restoration of the immune system. There have been extensive studies done on pathological conditions than actual aging itself. Aging and MSC were studied separately, but the similarities of the immune markers involved may come into convergence. The proliferative capacity and immunomodulatory function of MSCs could aid in the restoration of the immune cells and reduce the pro-inflammatory markers since these parameters are observed in aging as well. It is imperative to discuss the papers based on the aspects related to immunosenescence and inflammaging.

2. Mesenchymal Stem Cell Therapy to Reverse Aging Effects on the Immune System

According to The International Society for Cellular Therapy (ISCT) 2006, there are three minimal criteria for defining MSCs: “(i) MSC must be plastic-adherent when maintained in standard culture conditions. (ii) ≥95% of the MSC population must express CD105, CD73 and CD90, and ≤2% of the MSC population express of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA Class II surface molecules. (iii) MSC must differentiate to osteoblasts, adipocytes and chondroblasts in vitro.” [37].

MSCs lack MHC class II, which translates to low immunogenicity and allows both allogeneic and autologous MSC transplantation. Standardization and commercialization of allogeneic MSCs would be readily available at a reduced cost due to the lack of need to create a personalized cell therapy from the autologous source and the potential of expanding the cells in large-scale [38]. To date, MSCs have been used in clinical trials for osteoarthritis, spinal cord injury, diabetes mellitus, autoimmune disease (Crohn’s disease, multiple sclerosis, systemic lupus erythematosus, and systemic sclerosis), and systemic diseases such as graft-versus-host diseases and sepsis [30][39][40][41]. Additionally, MSCs also have been used to treat neonatal diseases, i.e., intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis [42].

2.1. Mechanism of MSCs Action on Immune System

Some evidences showed that the ameliorating effects of MSCs on the immune system are not due to direct engraftment and cell replacement, but rather paracrine manner and direct cell-to-cell contact [26][43]. MSCs secrete soluble paracrine factors including TGF-β, prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), hepatocyte growth factor (HGF), nitric oxide (NO), interferon-gamma (IFN-γ), IL-2, and IL-10, which produce an immunomodulatory effect. They also express FasL and PD-L1 for contact-dependent inhibition to induce T cell apoptosis [20][26]. MSCs express IL-10, which is an anti-inflammatory and immunoregulatory cytokine. Furthermore, they produce IL-6 and IL-8, which are known to be associated with MSC tissue repair potential [44]. Subsequently, MSCs control the inflammatory state as evidence of the reduced expression of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and CRP [45]. Then, the STAT6 pathway is activated by IL-4, which then stimulates the MSCs to

secrete TGF-β. This promotes the development of CD8+ T cells and Treg cells while suppressing the Th1 [46][47][48][49][50][51]. Moreover, MSC-secreted TGF-β has a role in macrophage polarization towards the M2 phenotype. These M2 macrophages stimulate the expression of IL-10, which alleviates inflammation. The macrophage phagocytic ability is also enhanced by TGF-β through Akt-FoxO1 pathway [36][52]. Table 1 shows the list of potential markers involved in inflammaging, which may be useful to determine the efficacy of MSC therapy.

Table 1. The potential 'inflammaging markers' related to inflammatory diseases and aging. These markers may be used to validate the efficacy of MSC treatment. ('↓' = decrease; '↑' = increase; '-' = no change).

Potential 'Inflammaging Markers'	Status in Inflammaging	References
IGF-1	↓	[17][53][54]
CD4+ T cells	↓	[19][55][56][57]
CD28+ T cells	↓	[11][58][59]
CD19+ B cells	↓	[60][61]
IL-10	↓/-	[2][35][62][63]
TGF-β	↓	[33][54][64][65]
IL-2	-	[66]
IFN-γ	↑	[66][67]
TNF-α	↑	[66][68][69]
IL-6	↑	[15][36][54][70][71]
WBC	↑	[17]
CD8+ T cells	↑	[19][55][56][57][72][58][73]
CD56+ NK cells	↑	[74][75][76][72][77][78]
IL-1β	↑/-	[36][69]
IL-15	↑	[69]
IL-18	↑	[69]
CD68	↑	[68]
MCP-1	↑	[68]
IL-17	↑	[34]
IL-8 (CXCL8)	↑	[11][74]

Potential 'Inflammaging Markers'	Status in Inflammaging	References
CXCL10	↑	[79][80]
CCL2	↑	[80][81]

ffects are cells is a antibody production of B cells, which in turn, may aid in the management of autoimmune conditions and graft rejections [82]. Moreover, Lee et al. noted that the xenogeneic transplantation of human MSCs (hMSCs) in SLE mice models only inhibited the T cells but not the B cells. However, hMSCs that are primed with IFN-γ have increased CXCL10 and IDO expression, which effectively attracts B cells for contact inhibition [45].

In a study by Shin et al., they found that adipose tissue-derived MSCs (AT-MSCs) treatment successfully prevented the ill-effects of sepsis by mitigating the systemic inflammation and multi-organ damage. They observed the drop in pro-inflammatory markers namely IL-6 and TNF-α and reduced damage in kidney, lungs, and liver [35]. During the treatment with MSCs, there is an increased expression in inflammatory cytokines including IL-1α, IL-1β, and IL-6. It is important to note that this increase is not associated with the severity of inflammation, but it is to prime the MSCs for a sustained immunosuppression [44].

The mechanism of action of MSCs on the immune system is not constitutively inhibitory, but is acquired after exposure to the inflammatory environment with IFN-γ. IFN-γ is one of the cytokines released by T cytotoxic cells during inflammation. Therefore, in Th17 centered inflammatory response, MSC treatment would require the addition of Treg to successfully regulate the inflammation [45][83]. Lim et al. found that combination of MSCs and Treg has shown promising results in IFN-γ knockout mice with reduced inflammation and IL-7 production [83]. Additionally, Fan et al. divulged that the IFN-γ stimulation could also induce a higher expression of galectin-9 (Gal-9) in the umbilical cord-derived MSCs (UC-MSCs) through the signal transducer and activator of transcription (STAT) and c-Jun N-terminal kinase (JNK) signaling pathways. Gal-9 is one of the constitutively expressed immunomodulatory components of MSCs, which acts by suppressing CD4+ T helper cells (Th1 and Th17) and CD8+ T cytotoxic cells and regulates the suppressive activity of Treg. Even so, when Gal-9 production is inhibited, MSCs could still exert its immunosuppressive function through paracrine manner [83]. Roux et al. also observed a significant reduction in the population of both CD4+ and CD8+ T lymphocytes post-treatment with human iPSC-derived MSCs. The immunosuppression on T cells by MSCs was further substantiated with the increased expression of LAG3 and CTLA4, and cytokines including IL-10, TGF-β, and LIF [44]. Li et al. observed a significant increase in CXCR3+ Tregs in the lungs and lymphoid tissues post-MSC infusion. MSCs also increased the production of CXCL9 and CXCL10 produced by lung phagocytes which mediate the recruitment of Tregs [34].

Anderson et al.'s experiment on mice has also shown that murine AT-MSCs reduced the severity of experimental autoimmune encephalomyelitis (EAE) in mice. It is achievable due to the inhibition of the autoimmune T cell response with no increase in foxp3 Tregs. Moreover, MSCs inhibited the maturation of DCs in vitro via COX-1/2 activity and also lowered the amount of activated DCs in the lymph nodes of EAE mice [84]. DCs from the older adults have increased reactivity to self-antigen, hence their constantly activated state produces proinflammatory cytokines and stimulates the proliferation of T cells [85]. Through the inhibition of DC maturation, the inflammatory state of EAE was managed. Moreover, a study by Liu et al. transplanting human UC-MSCs into mice model showed significant improvements in the EAE pathogenesis in which the transplantation stimulated spinal cord

remyelination and induced a shift of Th1 to Th2 [86]. Another study by Donders et al. using Wharton's jelly-derived MSCs (WJ-MSCs) also found reduction in signs and severity of EAE in rats. Nevertheless, they found that the ameliorating effects of MSCs were only temporary, and the transplanted rats will clinically deteriorate again. Although repeated dosages of MSCs were administered, the disease pathogenesis of EAE did not improve [87]. This contradicting data calls for more research data on the extent of MSC regenerative capability in clinical use. Table 2 shows the effect of MSC on the immune system in human clinical studies.

Table 2. A summary of clinical studies of MSC effects on the immune system from 2017–2021.

References	Human Subjects	MSC and Dosage	Results (Related to Immune Cells and Inflammatory Markers)	Additional Notes
Golpanian et al. (2017) [88]	An average age of 78.4 ± 4.7 years and Clinical Frailty Score of 4–6	Group 1 = 20 × 106 allo-hBM-MSCs, IV injection	Group 2 and Group 3 showed significant decrease in TNF-α, whereas Group 1 showed moderate reduction.	100×10^6 cells is the optimal dose level.
		Group 2 = 100 × 106 allo-hBM-MSCs, IV injection		
		Group 3 = 200 × 106 allo-hBM-MSCs, IV injection	No significant changes were seen in CRP, IL-6, fibrinogen, D-dimer, and white blood cell counts.	No additional benefit or loss of effect when 200 × 10^6 cell dose was used.
Tompkins et al. (2017) [89]	Age ≥60 and ≤95 years with Clinical Frailty Score of 4–7	Group 1 = 100 × 10^6 allo-hBM-MSCs, IV injection	Decreased serum TNF-α levels in Group 1.	No therapy-related side effects occurred.
			Decreased B cell intracellular TNF-α in both Group 1 and Group 2.	
			Decreased early CD 69 and late activated CD25 T cells in both Group 1 and Group 2.	
			Decreased CD8 in Group 2.	
		Group 2 = 200 × 10^6 allo-hBM-MSCs, IV injection	No changes in CD4 in both Group 1 and Group 2.	
			CD4/CD8 ratio increased in Group 2.	

References	Human Subjects	MSC and Dosage	Results (Related to Immune Cells and Inflammatory Markers)	Additional Notes
			No significant changes noted in IL-6, CRP, D-dimer, CBC, and fibrinogen in both Group 1 and Group 2.	
Chin et al. (2020) [90]	Healthy, non-frail subjects with mean age of 55 ± 13 years	Group 1: 65 × 10^6 allo-hUC-MSCs, IV injection	In Group 1, no significant changes were noted in the serum levels of IL-10, IL-1RA, IL-6, PGE2, and TNF-α.	No therapy-related side effects occurred.
			In Group 2, the serum IL-1RA level was significantly increased for at least 6 months post-infusion.	
			The serum IL-6 level throughout the 6 months monitoring period was higher in Group 2 than in Group 1.	The immunoglobulin E (IgE) level remained low within the normal range which indicated that there were no hypersensitivity reaction post-infusion.
		Group 2: 130 × 10^6 allo-hUC-MSCs, IV injection	The serum TNF-α level was significantly lower at day 2 in Group 2 than Group 1.	
			Both Group 1 and Group 2 observed a significant increase in C-reactive protein at day 2 post-infusion, which then dropped continuously over 6 months.	No significant changes in total white cell count or its subfractions post-infusion.
			The albumin/globulin ratio was higher in Group 2 than in Group 1 at 6 months.	No significant changes in the lung function tests (FEV1 and FEV1/FVC levels) post-infusion.
				No significant changes in the growth factors (VEGF, TGF-β, and HGF) level post-infusion.

References	Human Subjects	MSC and Dosage	Results (Related to Immune Cells and Inflammatory Markers)	Additional Notes
Hashemian et al. (2021) [91] [90]	11 patients diagnosed with COVID-19-induced ARDS who were admitted to the intensive care unit, age range was 42–66 years old	3 × IV injections (200 × 10^6 cells) every other day for a total of 600 × 10^6 hUC-MSCs (6 cases) or PL-MSCs (5 cases). [34][87]	Significant reductions in serum levels of TNF-α, IL-8 and CRP were seen in all six survivors.	All six survivors were well with no complaints of dyspnea on day 60 post-infusion.
			IL-6 levels decreased in five patients.	Radiological parameters of the lung CT scans showed great signs of recovery.
			IFN-γ levels decreased in four patients.	Four patients who had signs of multi-organ failure or sepsis died in average 10 days after the first MSC infusion.
			IL-4 and IL- 10 levels increased in four cases, but the differences were not statistically significant.	

ealthy cell
t not cell
nmences.
of Gal-9
[83]. Li et al.
observed
el of anti-
ever, note
ss of the
urvival of

2.2. Translational Application of MSCs

Bone marrow-derived MSCs (BM-MSCs) were the default source of MSCs. Nonetheless, the highly invasive procurement procedure, low cell yield (0.001–0.01% of bone marrow mononuclear cells) and multipotency that diminishes with donor age encouraged studies to be conducted on other sources of MSCs. Peripheral blood-derived MSCs (PB-MSCs) mobilized by the G-CSF are identical to BM-MSCs, but are more easily procured. However, both BM-MSCs and PB-MSCs have longer doubling time compared to MSCs from other sources [92]. PB-MSCs have been reported to possess the highest immunosuppressive capability among PB-MSCs, UC-MSCs, AT-MSCs and BM-MSCs [26]. However, contradictory results have been reported in others studies [40]. AT-MSCs can be obtained easily as surgical waste and lipo-aspirates at a high concentration up to 3% whereas UC-MSCs has the highest degree of multipotency than BM-MSCs and AT-MSCs [26].

FEV1—forced expiratory volume in one second, FVC—forced vital capacity, COVID-19—Coronavirus disease 2019, ARDS—Acute Respiratory Distress Syndrome, PL-MSCs—placental MSCs, CT—computed tomography.

To date, there is no definite evidence that suggests the best source of MSCs for clinical use. The sources are classified into adult and neonatal tissue derived, which have their advantages and disadvantages depending on its use. The heterogeneity among MSCs from different sources and the differences in cell treatment protocol make it impossible for direct comparison. Naturally, MSCs derived from perinatal tissues have stronger immunomodulatory properties compared to the aged source. UC-MSCs and WJ-MSCs are non-senescent, highly proliferative and with potent differentiation potential [26][93]. In application regarding immunosenescence, declining cellular functions and chronic sub-clinical inflammation are of concern in an aging person. Hence, allogenic UC-MSCs and WJ-MSCs seem more suited to be used in this subject matter. Nevertheless, the plasticity of UC-MSCs relies on the metabolic condition of the mother during pregnancy. UC-MSCs collected from gestational diabetes mellitus mothers displayed earlier cellular senescence and decreased cell growth [94]. Therefore, UC-MSCs should be sourced from healthy mothers to ensure a high biological quality of stem cells is obtained for clinical use. Abolhasani et al. also reported that the gestational age and in vitro expansion can influence the immunomodulatory properties of UC-MSCs [95].

Next, the optimal method of administering MSCs has yet to be determined. The MSCs can be introduced into the body locally or systematically. Local administration of MSCs targeted to the injury site and produced rapid results. However, there is a risk of cell death and bleeding at the site of application [96]. The systemic administration including intraperitoneal (IP), intravascular (IV), subcutaneous (SC), and intramuscular (IM) delivery have varying cell fate and therapeutic efficacy. Castelo-Branco et al. found that the IP method produced better homing and inflammation suppression than IV [33]. On the contrary, Gonçalves et al. contended that the IV administration of MSCs was more effective than IP method in the treatment of colitis as IV administration managed to stimulate a higher level of immunosuppression [97]. However, MSCs administered through the IV route tend to become entrapped in the lungs, with only 10% of the transplanted cells accumulate at the site of damage [34][96][98]. Roux et al. stated the preference of IP over IV as to avoid the risk of pulmonary embolization which may lead to the surge of an anti-inflammatory protein known as TSG6 [44]. IM injection is another possible route of MSC delivery which is advocated by Braid et al. for producing the longest cell retention time in the host body when compared to IV, IP, and SC, which was more than 100 days. Both IM and SC implantation sites also retained most of the MSCs, which shows a potential for controlled MSC dosage [98]. Furthermore, IM is less invasive than IV. Nonetheless, the research data on effects of IM administration of MSCs on the immune system is inadequate compared to the more established IV method.

Ueda et al. injected MSCs contained in collagen scaffold to the dorsum part of mice which considerably prolonged the retention of MSCs at the transplantation site for at least 2 weeks. The collagen scaffold acted as a reservoir for the exogenous MSCs and preserved the self-renewal, multipotency, and homing functions of MSCs. Furthermore, the formation of aggregates, which commonly occurs with IV administration can be avoided [96].

Ebrahim et al. compared the efficacy of standard treatment using antileukotriene drug (Montelukast) versus MSCs in the treatment of allergic rhinitis. MSCs exert immunomodulatory effects on the adaptive immunity by shifting the TH1/TH2 balance through T cell suppression and production of Treg. Rats treated with MSCs showed significant improvement in the allergic and inflammatory response and less damage to the nasal epithelium, which is superior compared the rats treated with antileukotriene drug [99]. El-Gendy et al. compared AT-MSCs with etanercept in terms of preventive and therapeutic efficacy in rheumatoid arthritis. Etanercept is an anti-inflammatory drug commonly prescribed for rheumatoid arthritis and other inflammatory conditions. The results of rats treated with both groups are comparable in terms of suppression of clinical signs, less severity of joint deformity, and modulation of immune responses. The etanercept group showed the lowest TNF-α level but the AT-MSCs group had significantly higher levels of Treg cells and IL-10 [100]. These results showed the promising prospect of MSCs to substitute the current prescription in improving inflammatory conditions.

Golpanian et al. and Tompkins et al. conducted the phase I and phase II clinical trials in aged patients by administering different doses of allogeneic MSCs through the IV route. The studies monitor the adverse effects as well as the patients' physical performances and TNF-α level for six months. Both studies demonstrated that 100 million allogenic MSCs is the most optimum dosage in frail patients which produced significant improvements in both physical and inflammaging condition, noting reduced circulating TNF-α level. Safety of IV administration of

allogeneic MSCs is also demonstrated when treatment emergent-serious adverse events are absent in the treated patients [89][88].

Zheng et al. plotted an extensive immune cell landscape in aging and COVID-19. In general, COVID-19 patients who are elderly have shown immune cell polarization and upregulation of inflammatory genes. There is a decrease in TCR and BCR diversity and an increase in clonality of effector, cytotoxic, and exhausted T cells. The NK cells and B cells have decreased antigen-presenting ability due to the upregulated inflammaging. Besides, the phenotype of mononuclear cells involved are inflammatory and persist at a higher ratio than the T cells. To add insult to the injury, aging also increases the expression of the COVID-19 susceptibility genes. Unsurprisingly, the elderly patients have lowered threshold of triggering cytokine storms and lymphopenia, which result in higher mortality from the infection [74]. MSC has been actively studied for COVID-19 treatment. Along with the urgency of the COVID-19 pandemic, numerous clinical trials have been proposed urgently to suggest MSC as an endogenous biological intervention to reduce the severity of the disease. At the time of writing, there are 53 clinical trials registered on the https://clinicaltrials.gov/ (accessed on 20 May 2021). In February 2020, a critically ill COVID-19 patient with severe pneumonia, ARDS and multi-organ injury was treated with hUCMSCs adoptive transfer therapy. Shortly after the treatment, their haematologic parameters, immune cell count, blood chemistry and clinical presentation of pneumonia vastly improved in a short time. After 8 days, the patient was discharged from the intensive care unit (ICU). Even though this study had only documented the recovery of one patient, it is remarkable that MSC may hold such premises [101]. Haberle et al. had also seen great improvement in their MSC treatment group. At the start of the study, the selected MSC treatment group had more severe COVID-19 ARDS than the control group, as indicated by the higher Murray score for lung injury. Finally, the MSC group showed significantly better pulmonary function and reduced inflammatory cells at discharge when compared to the control group [102]. Hashemian et al. also reported a significant decrease in the major inflammatory biomarkers (CRP, IL-6, IL-8, and TNF-α) and a significant improvement in the opacities of the lung CT scans after the MSC infusions [91].

References

1. Aspinall, R.; del Giudice, G.; Effros, R.B.; Grubeck-Loebenstein, B.; Sambhara, S. Challenges for vaccination in the elderly. Immun. Ageing 2007, 4, 9.
2. Hsieh, T.-H.; Tsai, T.-T.; Chen, C.-L.; Shen, T.-J.; Jhan, M.-K.; Tseng, P.-C.; Lin, C.-F. Senescence in monocytes facilitates dengue virus infection by increasing infectivity. Front. Cell. Infect. Microbiol. 2020, 10, 375.
3. Bewick, T.; Sheppard, C.; Greenwood, S.; Slack, M.; Trotter, C.; George, R.; Lim, W.S. Serotype prevalence in adults hospitalised with pneumococcal non-invasive community-acquired pneumonia. Thorax 2012, 67, 540–545.
4. Ochoa-Gondar, O.; Vila-Córcoles, A.; de Diego, C.; Arija, V.; Maxenchs, M.; Grive, M.; Martin, E.; Pinyol, J.L.; Vila-Córcoles, A.; Ansa, X.; et al. The burden of community-acquired pneumonia in

the elderly: The Spanish EVAN-65 study. BMC Public Health 2008, 8, 1–7.

5. Theodore, J.; Iwashyna, E.; Ely, E.W.; Dylan, M.; Smith, K.M.L. Long-term cognitive impairment and functional disability among survivors of severe sepsis. Yearb. Crit. Care Med. 2011, 2011, 188–190.
6. Martin-Loeches, I.; Guia, M.C.; Vallecoccia, M.S.; Suarez, D.; Ibarz, M.; Irazabal, M.; Ferrer, R.; Artigas, A. Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: A prospective, observational, multicenter cohort study. Ann. Intensive Care 2019, 9.
7. Borst, J.; Ahrends, T.; Bąbała, N.; Melief, C.J.M.; Kastenmüller, W. CD4+ T cell help in cancer immunology and immunotherapy. Nat. Rev. Immunol. 2018, 18, 635–647.
8. Lang, P.O.; Mendes, A.; Socquet, J.; Assir, N.; Govind, S.; Aspinall, R. Effectiveness of influenza vaccine in aging and older adults: Comprehensive analysis of the evidence. Clin. Interv. Aging 2012, 7, 55–64.
9. Weinberger, B. Vaccines for the elderly: Current use and future challenges. Immun. Ageing 2018, 15, 1–8.
10. Blasi, F.; Akova, M.; Bonanni, P.; Dartois, N.; Sauty, E.; Webber, C.; Torres, A. Community-acquired pneumonia in adults: Highlighting missed opportunities for vaccination. Eur. J. Intern. Med. 2017, 37, 13–18.
11. Rea, I.M.; Gibson, D.S.; McGilligan, V.; McNerlan, S.E.; Denis, H.A.; Ross, O.A. Age and age-related diseases: Role of inflammation triggers and cytokines. Front. Immunol. 2018, 9, 1.
12. Schulman, I.H.; Balkan, W.; Hare, J.M. Mesenchymal stem cell therapy for aging frailty. Front. Nutr. 2018, 5, 108.
13. Thomas, R.; Wang, W.; Su, D.M. Contributions of age-related thymic involution to immunosenescence and inflammaging. Immun. Ageing 2020, 17, 1–17.
14. Department of Economic and Social Affairs of the United Nations. World Population Ageing 2019; United Nations Department of Economic and Social Affairs: New York, NY, USA, 2019; ISBN 9789211483253.
15. Pansarasa, O.; Pistono, C.; Davin, A.; Bordoni, M.; Mimmi, M.C.; Guaita, A.; Cereda, C. Altered immune system in frailty: Genetics and diet may influence inflammation. Ageing Res. Rev. 2019, 54.
16. Álvarez, S.; Brañas, F.; Sánchez-Conde, M.; Moreno, S.; de Quirós, J.C.L.-B.; Muñoz-Fernández, M.Á. Frailty, markers of immune activation and oxidative stress in HIV infected elderly. PLoS ONE 2020, 15, e0230339.
17. Yao, X.; Li, H.; Leng, S.X. Inflammation and immune system alterations in frailty. Clin. Geriatr. Med. 2011, 27, 79–87.

18. Gautam, N.; Das, S.; Mahapatra, S.K.; Chakraborty, S.P.; Kundu, P.K.; Roy, S. Age-associated oxidative damage in llymphocytes. Oxid. Med. Cell. Longev. 2010, 3, 275–282.
19. El-Kader, S.M.A.; Al-Shreef, F.M. Inflammatory cytokines and immune system modulation by aerobic versus resisted exercise training for elderly. Afr. Health Sci. 2018, 18, 120.
20. Larrick, J.W.; Mendelsohn, A.R. Mesenchymal stem cells for frailty? Rejuvenation Res. 2017, 20, 525–529.
21. De Vita, F.; Lauretani, F.; Bauer, J.; Bautmans, I.; Shardell, M.; Cherubini, A.; Bondi, G.; Zuliani, G.; Bandinelli, S.; Pedrazzoni, M.; et al. Relationship between vitamin D and inflammatory markers in older individuals. Age 2014, 36, 1–13.
22. He, K.; Liu, K.; Daviglus, M.L.; Jenny, N.S.; Mayer-Davis, E.; Jiang, R.; Steffen, L.; Siscovick, D.; Tsai, M.; Herrington, D. Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the multi-ethnic study of atherosclerosis [MESA]). Am. J. Cardiol. 2009, 103, 1238–1243.
23. Zhang, Y.; Xu, X.J.; Lian, T.Y.; Huang, L.F.; Zeng, J.M.; Liang, D.M.; Yin, M.J.; Huang, J.X.; Xiu, L.C.; Yu, Z.W.; et al. Development of frailty subtypes and their associated risk factors among the community-dwelling elderly population. Aging 2020, 12, 1128–1140.
24. Ng, T.P.; Feng, L.; Nyunt, M.S.Z.; Feng, L.; Niti, M.; Tan, B.Y.; Chan, G.; Khoo, S.A.; Chan, S.M.; Yap, P.; et al. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: A randomized controlled trial. Am. J. Med. 2015, 128, 1225–1236.
25. Apóstolo, J.; Cooke, R.; Bobrowicz-Campos, E.; Santana, S.; Marcucci, M.; Cano, A.; Vollenbroek-Hutten, M.; Germini, F.; D'Avanzo, B.; Gwyther, H.; et al. Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: A systematic review. JBI Database Syst. Rev. Implement. Rep. 2018, 16, 140–232.
26. Mushahary, D.; Spittler, A.; Kasper, C.; Weber, V.; Charwat, V. Isolation, cultivation, and characterization of human mesenchymal stem cells. Cytom. Part A 2018, 93, 19–31.
27. Hafez, P.; Chowdhury, S.R.; Jose, S.; Law, J.X.; Ruszymah, B.H.I.; Ramzisham, A.R.M.; Ng, M.H. Development of an in vitro cardiac ischemic model using primary human cardiomyocytes. Cardiovasc. Eng. Technol. 2018, 9, 529–538.
28. Lokanathan, Y.; Law, J.X.; Yazid, M.D.; Chowdhury, S.R.; Busra, M.F.M.; Sulaiman, N.; Ng, A.M.H. 8. mesenchymal stem cells and their role in hypoxia-induced injury. In Stem Cells: From Myth to Reality and Evolving; De Gruyter: Berlin, Germany; Boston, MA, USA, 2019; pp. 166–186.
29. Looi, Q.H.; Eng, S.P.; Liau, L.L.; Tor, Y.S.; Bajuri, M.Y.; Ng, M.H.; Law, J.X. Mesenchymal stem cell therapy for sports injuries-From research to clinical practice. Sains Malaysiana 2020, 49, 825–838.

30. Rizvanov, A.A.; Persson, J.; Şahin, F.; Bellusci, S.; Oliveira, P.J. Hematopoietic and mesenchymal stem cells in biomedical and clinical applications. Stem Cells Int. 2016, 2016.
31. Fafián-Labora, J.A.; Morente-López, M.; Arufe, M.C. Effect of aging on behaviour of mesenchymal stem cells. World J. Stem Cells 2019, 11, 337–346.
32. Crippa, S.; Bernardo, M.E. Mesenchymal stromal cells: Role in the BM niche and in the support of hematopoietic stem cell transplantation. HemaSphere 2018, 2.
33. Castelo-Branco, M.T.L.; Soares, I.D.P.; Lopes, D.V.; Buongusto, F.; Martinusso, C.A.; do Rosario, A.; Souza, S.A.L.; Gutfilen, B.; Fonseca, L.M.B.; Elia, C.; et al. Intraperitoneal but not intravenous cryopreserved mesenchymal stromal cells home to the inflamed colon and ameliorate experimental colitis. PLoS ONE 2012, 7.
34. Li, W.; Chen, W.; Huang, S.; Yao, G.; Tang, X.; Sun, L. Mesenchymal stem cells prevent overwhelming inflammation and reduce infection severity via recruiting CXCR3 + regulatory T cells. Clin. Transl. Immunol. 2020, 9, 1–15.
35. Shin, S.; Kim, Y.; Jeong, S.; Hong, S.; Kim, I.; Lee, W.; Choi, S. The therapeutic effect of human adult stem cells derived from adipose tissue in endotoxemic rat model. Int. J. Med. Sci. 2012, 10, 8–18.
36. Liu, F.; Qiu, H.; Xue, M.; Zhang, S.; Zhang, X.; Xu, J.; Chen, J.; Yang, Y.; Xie, J. MSC-secreted TGF-β regulates lipopolysaccharide-stimulated macrophage M2-like polarization via the Akt/FoxO1 pathway. Stem Cell Res. Ther. 2019, 10, 1–14.
37. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.C.; Krause, D.S.; Deans, R.J.; Keating, A.; Prockop, D.J.; Horwitz, E.M. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cytotherapy 2006, 8, 315–317.
38. Hassan, M.N.F.B.; Yazid, M.D.; Yunus, M.H.M.; Chowdhury, S.R.; Lokanathan, Y.; Idrus, R.B.H.; Ng, A.M.H.; Law, J.X. Large-scale expansion of human mesenchymal stem cells. Stem Cells Int. 2020, 2020, 9529465.
39. Liau, L.L.; Looi, Q.H.; Chia, W.C.; Subramaniam, T.; Ng, M.H.; Law, J.X. Treatment of spinal cord injury with mesenchymal stem cells. Cell Biosci. 2020, 10, 112.
40. Liau, L.L.; Ruszymah, B.H.I.; Ng, M.H.; Law, J.X. Characteristics and clinical applications of Wharton's jelly-derived mesenchymal stromal cells. Curr. Res. Transl. Med. 2020, 68, 5–16.
41. Liau, L.L.; Looi, Q.H.; Eng, S.P.; Yazid, M.D.; Sulaiman, N.; Busra, M.F.M.; Ng, M.H.; Law, J.X. Mesenchymal stem cells for the treatment of immune-mediated diseases. In Stem Cells; World Scientific: Singapore, 2020; pp. 178–210. ISBN 978-981-12-0552-1.

42. Liau, L.L.; Al-Masawa, M.E.; Koh, B.; Looi, Q.H.; Foo, J.B.; Lee, S.H.; Cheah, F.C.; Law, J.X. The potential of mesenchymal stromal cell as therapy in neonatal diseases. Front. Pediatr. 2020, 8, 591693.

43. Rojas, M.; Xu, J.; Woods, C.R.; Mora, A.L.; Spears, W.; Roman, J.; Brigham, K.L. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. Am. J. Respir. Cell Mol. Biol. 2005, 33, 145–152.

44. Roux, C.; Saviane, G.; Pini, J.; Belaïd, N.; Dhib, G.; Voha, C.; Ibáñez, L.; Boutin, A.; Mazure, N.M.; Wakkach, A.; et al. Immunosuppressive mesenchymal stromal cells derived from human-induced pluripotent stem cells induce human regulatory T cells in vitro and in vivo. Front. Immunol. 2018, 8.

45. Lee, H.K.; Kim, E.Y.; Kim, H.S.; Park, E.J.; Lee, H.J.; Lee, T.Y.; Kim, K.S.; Bae, S.C.; Hong, J.T.; Kim, Y.; et al. Effect of human mesenchymal stem cells on xenogeneic T and B cells isolated from lupus-prone MRL.Fas lpr mice. Stem Cells Int. 2020, 2020.

46. Tinoco, R.; Alcalde, V.; Yang, Y.; Sauer, K.; Zuniga, E.I. Cell-intrinsic transforming growth factor-β signaling mediates virus-specific CD8+ T cell deletion and viral persistence in vivo. Immunity 2009, 31, 145–157.

47. Ouyang, W.; Oh, S.A.; Ma, Q.; Bivona, M.R.; Zhu, J.; Li, M.O. TGF-β cytokine signaling promotes CD8+ T cell development and low-affinity CD4+ T cell homeostasis by regulation of interleukin-7 receptor α expression. Immunity 2013, 39, 335–346.

48. Takimoto, T.; Wakabayashi, Y.; Sekiya, T.; Inoue, N.; Morita, R.; Ichiyama, K.; Takahashi, R.; Asakawa, M.; Muto, G.; Mori, T.; et al. Smad2 and Smad3 are redundantly essential for the TGF-β-mediated regulation of regulatory T plasticity and Th1 development. J. Immunol. 2010, 185, 842–855.

49. Li, M.O.; Wan, Y.Y.; Flavell, R.A. T cell-produced transforming growth factor-β1 controls T cell tolerance and regulates Th1- and Th17-cell differentiation. Immunity 2007, 26, 579–591.

50. Bettelli, E.; Carrier, Y.; Gao, W.; Korn, T.; Strom, T.B.; Oukka, M.; Weiner, H.L.; Kuchroo, V.K. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006, 441, 235–238.

51. Li, Y.; Liu, W.; Guan, X.; Truscott, J.; Creemers, J.W.; Chen, H.-L.; Pesu, M.; El Abiad, R.G.; Karacay, B.; Urban, J.F.; et al. STAT6 and furin are successive triggers for the production of TGF-β by T cells. J. Immunol. 2018, 201, 2612–2623.

52. Li, Y.; Sheng, Q.; Zhang, C.; Han, C.; Bai, H.; Lai, P.; Fan, Y.; Ding, Y.; Dou, X. STAT6 up-regulation amplifies M2 macrophage anti-inflammatory capacity through mesenchymal stem cells. Int. Immunopharmacol. 2021, 91, 107266.

53. Leng, S.X.; Cappola, A.R.; Andersen, R.E.; Blackman, M.R.; Koenig, K.; Blair, M.; Walston, J.D. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. Aging Clin. Exp. Res. 2004, 16, 153–157.

54. Cardoso, A.L.; Fernandes, A.; Aguilar-Pimentel, J.A.; de Angelis, M.H.; Guedes, J.R.; Brito, M.A.; Ortolano, S.; Pani, G.; Athanasopoulou, S.; Gonos, E.S.; et al. Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases. Ageing Res. Rev. 2018, 47, 214–277.

55. Sanderson, S.L.; Simon, A.K. In aged primary T cells, mitochondrial stress contributes to telomere attrition measured by a novel imaging flow cytometry assay. Aging Cell 2017, 16, 1234–1243.

56. Salminen, A.; Kaarniranta, K.; Kauppinen, A. Immunosenescence: The potential role of myeloid-derived suppressor cells (MDSC) in age-related immune deficiency. Cell. Mol. Life Sci. 2019, 76, 1901–1918.

57. Lelic, A.; Verschoor, C.P.; Ventresca, M.; Parsons, R.; Evelegh, C.; Bowdish, D.; Betts, M.R.; Loeb, M.B.; Bramson, J.L. The polyfunctionality of human memory CD8+ T cells elicited by acute and chronic virus infections is not influenced by age. PLoS Pathog. 2012, 8, e10.

58. Fülöp, T.; Larbi, A.; Pawelec, G. Human T cell aging and the impact of persistent viral infections. Front. Immunol. 2013, 4, 271.

59. Almanzar, G.; Schwaiger, S.; Jenewein, B.; Keller, M.; Herndler-Brandstetter, D.; Würzner, R.; Schönitzer, D.; Grubeck-Loebenstein, B. Long-term cytomegalovirus infection leads to significant changes in the composition of the CD8+ T-cell repertoire, which may be the basis for an imbalance in the cytokine production profile in elderly persons. J. Virol. 2005, 79, 3675–3683.

60. Duggal, N.A.; Upton, J.; Phillips, A.C.; Sapey, E.; Lord, J.M. An age-related numerical and functional deficit in CD19+CD24hiCD38hi B cells is associated with an increase in systemic autoimmunity. Aging Cell 2013, 12, 873–881.

61. Morbach, H.; Eichhorn, E.M.; Liese, J.G.; Girschick, H.J. Reference values for B cell subpopulations from infancy to adulthood. Clin. Exp. Immunol. 2010, 162, 271–279.

62. Garrido, A.; Cruces, J.; Ceprián, N.; Vara, E.; de la Fuente, M. Oxidative-inflammatory stress in immune cells from adult mice with premature aging. Int. J. Mol. Sci. 2019, 20, 769.

63. Zhang, J.Z.; Liu, Z.; Liu, J.; Ren, J.X.; Sun, T.S. Mitochondrial DNA induces inflammation and increases TLR9/NF-κB expression in lung tissue. Int. J. Mol. Med. 2014.

64. Liu, C.; Zhang, Y.S.; Chen, F.; Wu, X.Y.; Zhang, B.B.; Wu, Z.D.; Lei, J.X. Immunopathology in schistosomiasis is regulated by TLR2,4- and IFN-γ-activated MSC through modulating Th1/Th2 responses. Stem Cell Res. Ther. 2020, 11, 1–10.

65. Tominaga, K.; Suzuki, H.I. TGF-β signaling in cellular senescence and aging-related pathology. Int. J. Mol. Sci. 2019, 20, 5002.

66. McNerlan, S.E.; Rea, I.M.; Alexander, H.D. A whole blood method for measurement of intracellular TNF-α, IFN-γ and IL-2 expression in stimulated CD3 + lymphocytes: Differences between young and elderly subjects. Exp. Gerontol. 2002, 37, 227–234.

67. Aso, K.; Tsuruhara, A.; Takagaki, K.; Oki, K.; Ota, M.; Nose, Y.; Tanemura, H.; Urushihata, N.; Sasanuma, J.; Sano, M.; et al. Adipose-derived mesenchymal stem cells restore impaired mucosal immune responses in aged mice. PLoS ONE 2016, 11, 1–15.

68. Han, J.H.; Kim, O.H.; Lee, S.C.; Kim, K.H.; Park, J.H.; Lee, J.I.; Lee, K.H.; Hong, H.E.; Seo, H.; Choi, H.J.; et al. A novel hepatic anti-fibrotic strategy utilizing the secretome released from etanercept-synthesizing adipose-derived stem cells. Int. J. Mol. Sci. 2019, 20, 6302.

69. Adams, A.A.; Breathnach, C.C.; Katepalli, M.P.; Kohler, K.; Horohov, D.W. Advanced age in horses affects divisional history of T cells and inflammatory cytokine production. Mech. Ageing Dev. 2008, 129, 656–664.

70. De Macedo, B.G.; de Oliveira, H.S.C.; de Paula, M.V.; de Gomes, G.C.; de Antunes, C.M.F. Association between inflammatory mediators, grip strength and mobility in community-dwelling elderly. Fisioterapia em Movimento 2018, 31, 3132.

71. Lustig, A.; Liu, H.B.; Metter, E.J.; An, Y.; Swaby, M.A.; Elango, P.; Ferrucci, L.; Hodes, R.J.; Weng, N.P. Telomere shortening, inflammatory cytokines, and anti-cytomegalovirus antibody follow distinct age-associated trajectories in humans. Front. Immunol. 2017, 8.

72. Plonquet, A.; Bastuji-Garin, S.; Tahmasebi, F.; Brisacier, C.; Ledudal, K.; Farcet, J.P.; Paillaud, E. Immune risk phenotype is associated with nosocomial lung infections in elderly in-patients. Immun. Ageing 2011, 8, 8.

73. Zacca, E.R.; Crespo, M.I.; Acland, R.P.; Roselli, E.; Núñez, N.G.; Maccioni, M.; Maletto, B.A.; Pistoresi-Palencia, M.C.; Morón, G. Aging impairs the ability of conventional dendritic cells to cross-prime CD8+ T cells upon stimulation with a TLR7 ligand. PLoS ONE 2015, 10, 1–20.

74. Zheng, Y.; Liu, X.; Le, W.; Xie, L.; Li, H.; Wen, W.; Wang, S.; Ma, S.; Huang, Z.; Ye, J.; et al. A human circulating immune cell landscape in aging and COVID-19. Protein Cell 2020, 11, 740–770.

75. Shitara, S.; Hara, T.; Liang, B.; Wagatsuma, K.; Zuklys, S.; Holländer, G.A.; Nakase, H.; Chiba, T.; Tani-ichi, S.; Ikuta, K. IL-7 produced by thymic epithelial cells plays a major role in the development of thymocytes and TCRγδ + intraepithelial lymphocytes. J. Immunol. 2013, 190, 6173–6179.

76. Gounder, S.S.; Abdullah, B.J.J.; Radzuanb, N.E.I.B.M.; Zain, F.D.B.M.; Sait, N.B.M.; Chua, C.; Subramani, B. Effect of aging on NK cell population and their proliferation at ex vivo culture

condition. Anal. Cell. Pathol. 2018, 2018.

77. Hazeldine, J.; Lord, J.M. The impact of ageing on natural killer cell function and potential consequences for health in older adults. Ageing Res. Rev. 2013, 12, 1069–1078.
78. Benabdallah, B.; Désaulniers-Langevin, C.; Colas, C.; Li, Y.; Rousseau, G.; Guimond, J.V.; Haddad, E.; Beauséjour, C. Natural killer cells prevent the formation of teratomas derived from human induced pluripotent stem cells. Front. Immunol. 2019, 10, 1–9.
79. Fan, J.; Tang, X.; Wang, Q.; Zhang, Z.; Wu, S.; Li, W.; Liu, S.; Yao, G.; Chen, H.; Sun, L. Mesenchymal stem cells alleviate experimental autoimmune cholangitis through immunosuppression and cytoprotective function mediated by galectin-9. Stem Cell Res. Ther. 2018, 9, 1–12.
80. Antonelli, A.; Rotondi, M.; Fallahi, P.; Ferrari, S.M.; Paolicchi, A.; Romagnani, P.; Serio, M.; Ferrannini, E. Increase of CXC chemokine CXCL10 and CC chemokine CCL2 serum levels in normal ageing. Cytokine 2006, 34, 32–38.
81. Seidler, S.; Zimmermann, H.W.; Bartneck, M.; Trautwein, C.; Tacke, F. Age-dependent alterations of monocyte subsets and monocyte-related chemokine pathways in healthy adults. BMC Immunol. 2010, 11.
82. Rosado, M.M.; Bernardo, M.E.; Scarsella, M.; Conforti, A.; Giorda, E.; Biagini, S.; Cascioli, S.; Rossi, F.; Guzzo, I.; Vivarelli, M.; et al. Inhibition of B-cell proliferation and antibody production by mesenchymal stromal cells is mediated by T cells. Stem Cells Dev. 2015, 24, 93–103.
83. Lim, J.Y.; Park, M.J.; Im, K.I.; Kim, N.; Jeon, E.J.; Kim, E.J.; La Cho, M.; Cho, S.G. Combination cell therapy using mesenchymal stem cells and regulatory T-cells provides a synergistic immunomodulatory effect associated with reciprocal regulation of Th1/Th2 and Th17/Treg cells in a murine acute graft-versus-host disease model. Cell Transplant. 2014, 23, 703–714.
84. Anderson, P.; Gonzalez-Rey, E.; O'Valle, F.; Martin, F.; Oliver, F.J.; Delgado, M. Allogeneic adipose-derived mesenchymal stromal cells ameliorate experimental eutoimmune encephalomyelitis by regulating self-reactive T cell responses and dendritic cell function. Stem Cells Int. 2017, 2017.
85. Agrawal, A.; Tay, J.; Ton, S.; Agrawal, S.; Gupta, S. Increased reactivity of dendritic cells from aged subjects to self-antigen, the human DNA. J. Immunol. 2009, 182, 1138–1145.
86. Liu, R.; Zhang, Z.; Lu, Z.; Borlongan, C.; Pan, J.; Chen, J.; Qian, L.; Liu, Z.; Zhu, L.; Zhang, J.; et al. Human umbilical cord stem cells ameliorate experimental autoimmune encephalomyelitis by regulating immunoinflammation and remyelination. Stem Cells Dev. 2013, 22, 1053–1062.
87. Donders, R.; Vanheusden, M.; Bogie, J.F.J.; Ravanidis, S.; Thewissen, K.; Stinissen, P.; Gyselaers, W.; Hendriks, J.J.A.; Hellings, N. Human Wharton's jelly-derived stem cells display

immunomodulatory properties and transiently improve rat experimental autoimmune encephalomyelitis. Cell Transplant. 2015, 24, 2077–2098.

88. Golpanian, S.; Difede, D.L.; Khan, A.; Schulman, I.H.; Landin, A.M.; Tompkins, B.A.; Heldman, A.W.; Miki, R.; Goldstein, B.J.; Mushtaq, M.; et al. Allogeneic human mesenchymal stem cell infusions for aging frailty. J. Gerontol. 2017, 72, 1505–1512.
89. Tompkins, B.A.; Difede, D.L.; Khan, A.; Landin, A.M.; Schulman, I.H.; Pujol, M.V.; Heldman, A.W.; Miki, R.; Goldschmidt-Clermont, P.J.; Goldstein, B.J.; et al. Allogeneic mesenchymal stem cells ameliorate aging frailty: A phase II randomized, double-blind, placebo-controlled clinical trial. J. Gerontol. 2017, 72, 1513–1521.
90. Chin, S.P.; Mohd-Shahrizal, M.Y.; Liyana, M.Z.; Then, K.Y.; Cheong, S.K. High dose of intravenous allogeneic umbilical cord-derived mesenchymal stem cells (CLV-100) infusion displays better immunomodulatory effect among healthy volunteers: A phase 1 clinical study. Stem Cells Int. 2020, 2020, 4–8.
91. Hashemian, S.M.R.; Aliannejad, R.; Zarrabi, M.; Soleimani, M.; Vosough, M.; Hosseini, S.E.; Hossieni, H.; Keshel, S.H.; Naderpour, Z.; Hajizadeh-Saffar, E.; et al. Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: A case series. Stem Cell Res. Ther. 2021, 12, 1–12.
92. Berebichez-Fridman, R.; Montero-Olvera, P.R. Sources and clinical applications of mesenchymal stem cells state-of-the-art review. Sultan Qaboos Univ. Med. J. 2018, 18, e264–e277.
93. Kim, J.H.; Jo, C.H.; Kim, H.R.; Hwang, Y.-I. Comparison of immunological characteristics of mesenchymal stem cells from the periodontal ligament, umbilical cord, and adipose tissue. Stem Cells Int. 2018, 2018.
94. Arutyunyan, I.; Elchaninov, A.; Makarov, A.; Fatkhudinov, T. Umbilical cord as prospective source for mesenchymal stem cell-based therapy. Stem Cells Int. 2016, 2016.
95. Abolhasani, M.; Rezaee, M.A.; Mohammadi, M.; Ghadimi, T.; Mohammadi, M.; Rahmani, M.R. Immunomodulatory properties of umbilical cord vein mesenchymal stromal cells influenced by gestational age and in vitro expansion. Immunol. Lett. 2018, 194, 62–68.
96. Ueda, N.; Atsuta, I.; Ayukawa, Y.; Yamaza, T.; Furuhashi, A.; Narimatsu, I.; Matsuura, Y.; Kondo, R.; Watanabe, Y.; Zhang, X.; et al. Novel application method for mesenchymal stem cell therapy utilizing its attractant-responsive accumulation property. Appl. Sci. 2019, 9, 4908.
97. Gonçalves, F.D.C.; Schneider, N.; Pinto, F.O.T.; Meyer, F.S.; Visioli, F.; Pfaffenseller, B.; Lopez, P.L.D.C.; Passos, E.P.A.; Cirne-Lima, E.O.B.; Meurer, L.; et al. Intravenous vs. intraperitoneal mesenchymal stem cells administration: What is the best route for treating experimental colitis? World J. Gastroenterol. 2014, 20, 18228–18239.

98. Braid, L.R.; Wood, C.A.; Wiese, D.M.; Ford, B.N. Intramuscular administration potentiates extended dwell time of mesenchymal stromal cells compared to other routes. Cytotherapy 2018, 20, 232–244.
99. Ebrahim, N.; Mandour, Y.M.H.; Farid, A.S.; Nafie, E.; Mohamed, A.Z.; Safwat, M.; Taha, R.; Sabry, D.; Sorour, S.M.; Refae, A. Adipose tissue-derived mesenchymal stem cell modulates the immune response of allergic rhinitis in a rat model. Int. J. Mol. Sci. 2019, 20, 873.
100. El-Gendy, H.; Hawass, S.E.D.; Awad, M.; Mohsen, M.A.; Amin, M.; Abdalla, H.A.; Fouad, S.; Lotfy, A. Comparative study between human mesenchymal stem cells and etanercept as immunomodulatory agents in rat model of rheumatoid arthritis. Immunol. Res. 2020, 68, 255–268.
101. Liang, B.; Chen, J.; Li, T.; Wu, H.; Yang, W.; Li, Y.; Li, J.; Yu, C.; Nie, F.; Ma, Z.; et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells. Chin. J. Tissue Eng. Res. 2020.
102. Häberle, H.; Magunia, H.; Lang, P.; Gloeckner, H.; Körner, A.; Koeppen, M.; Backchoul, T.; Malek, N.; Handgretinger, R.; Rosenberger, P.; et al. Mesenchymal stem cell therapy for severe COVID-19 ards. J. Intensive Care Med. 2021.