IJPSR (2022), Volume 13, Issue 11 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 February 2022; received in revised form, 07 May 2022; accepted, 26 May 2022; published 01 November 2022

MESENCHYMAL STEM CELLS (MSCS) AS POTENTIAL SOURCES OF TREATMENT OF NEURODEGENERATION DISEASE: A STRATEGIC REVIEW

Shreya Shreshtha [1], Rahul Verma [2], Shubham [3], T. S. Gopenath [1] and Kanthesh M. Basalingappa [*1]

Division of Molecular Biology [1], Department of Biotechnology and Bioinformatics, Faculty of Life Sciences, JSS Academy of Higher Education and Research, Mysuru - 570015, Karnataka, India.
Dr. B. R. Ambedkar Center for Biomedical Research [2], University of Delhi, New Delh - 110007, Delhi, India.
Department of Human Genetics [3], Guru Nanak Dev University, Amritsar - 143005, Punjab, India.

Keywords:

Mesenchymal stem cells (MSCs), multipotent, Umbilical cord, Bone marrow, Macrophages, Neurological disorders, Inflammation

Correspondence to Author:
Dr. Kanthesh M. Basalingappa

Assistant Professor,
Division of Molecular Biology,
Faculty of Life Sciences, JSS Academy of Higher Education and Research, Mysuru - 570015, Karnataka, India.

E-mail: kantheshmb@jssuni.edu.in

ABSTRACT: Mesenchymal Stem Cells are multipotent adult stem cells that are found in tissues of the body, including umbilical lines, bone marrow, fat cells, *etc*. Mesenchymal stem cells incline to self–restore tissues, such as bone, fat cells, connective tissues, and microglia cells, which are obtained from the mesoderm layer and act as macrophages in the central nervous system. So, MSCs can be used to promote functional recovery in many neurological disorders. Neuroinflammation is a pathological feature of neurodegenerative diseases, which is also indicated to mediate neuronal damage and deteriorate the backward accumulation of Aβ in Alzheimer's disease. The mechanism for MSC-based therapy in Alzheimer's disease that MSCs regulate neuroinflammation by microglia activation; this will reduce pathological features such as tau hyperphosphorylation and Aβ deposits and save the spatial learning and memory deficits and their multipotentiality and secretome, based on these findings include cell therapy methods for Parkinson disease mainly focused on the ability of stem cells to differentiate into Dopaminergic neurons producing cells that will replace diseased Dopaminergic neurons. MSC-based therapeutics have been suggested for osteoarthritis. MSCs were mostly found in a thin layer of connective tissue called periosteum, lungs, milk teeth, tendon, synovial stratum, cancellous bone, adipose tissue, tendon, lung, and other tissues. MSCs associated with immune cells and have immunomodulatory effects. Moreover, the RAP1/NFkb signalling pathway controls MSC paracrine activity, which seems to be linked with Female infertility. This review will assist you in understanding many aspects of MSC and its molecular role and therapeutic applications.

INTRODUCTION: MSCs can be utilized to advance useful recuperation in numerous neurological issues. MSCs can likewise lessen provocative reactions by different dissolvable elements. Amidst these variables, TNF alpha – working as a crucial factor impacting properties of immunomodulatory of MSCs.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(11).4254-68

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(11).4254-68

Accordingly, the specific component that causes hostile to – provocative impacts is unknown. In this investigation, we uncover that advanced M2 polarization through microglia *via* TSG-6 subsequently gives an enemy of the neuroinflammatory effects.

And in comparison to pluripotent stem cells, which have the risk of immune rejection and teratoma formation, adult stem cells, particularly mesenchymal stem cells (MSCs), are promoted as a suitable alternative because they also exhibit pluripotent properties. MSCs are also distinct from hematopoietic stem cells and can differentiate into

multiple cell types such as adipocytes, chondrocytes, and osteoblasts. Mesenchymal stem cells are spindle-shaped cells, first derived in the bone marrow of the mid-1970s [1]. These cells are found in various adult tissues and secretions, including adipose tissues, amniotic fluid, dental pulp, menstrual blood, placenta, endometrium, umbilical cord, and foetal tissues like liver and bone marrow, blood [2]. MSCs are also known for their multiple effective properties like self-regeneration, self-replication, and self-repairment [2, 3]. These cells help in the regulation of cells and a standard cell source of tissue renewal [1, 4]. MSCs also explicit definite cell biomarkers like CD73, CD90 and CD105, which can be diversified into, chondrogenic and osteogenic lineages *in-vitro* but deficient in CD14, CD19, CD34, and CD45 [5]. MSCs have immunomodulatory characteristics, which is one of their key benefits. *In-vitro* produced MSCs have the ability to interact with and influence the activity of the majority of effector cells engaged in the primary and acquired immune response mechanisms. They suppress complement-mediated proliferation of peripheral blood mononuclear cells, prevent apoptosis of native and activated neutrophils, and reduce the number of neutrophils attaching to vascular endothelial cells, restricting the mobilization of these cells to the location of injury [6].

MSCs regulate the whole tissue renewal mechanism by activating or suppressing the immune system once damaged tissues or cells. Toll-like receptors are one of the properties of MSCs, which help detect the threat. All the MSCs express TLR2, TLR3, TLR4, TLR7, and TLR9. The expression levels of these TLRs differ greatly depending on the tissue from which they originate **Fig. 1.**

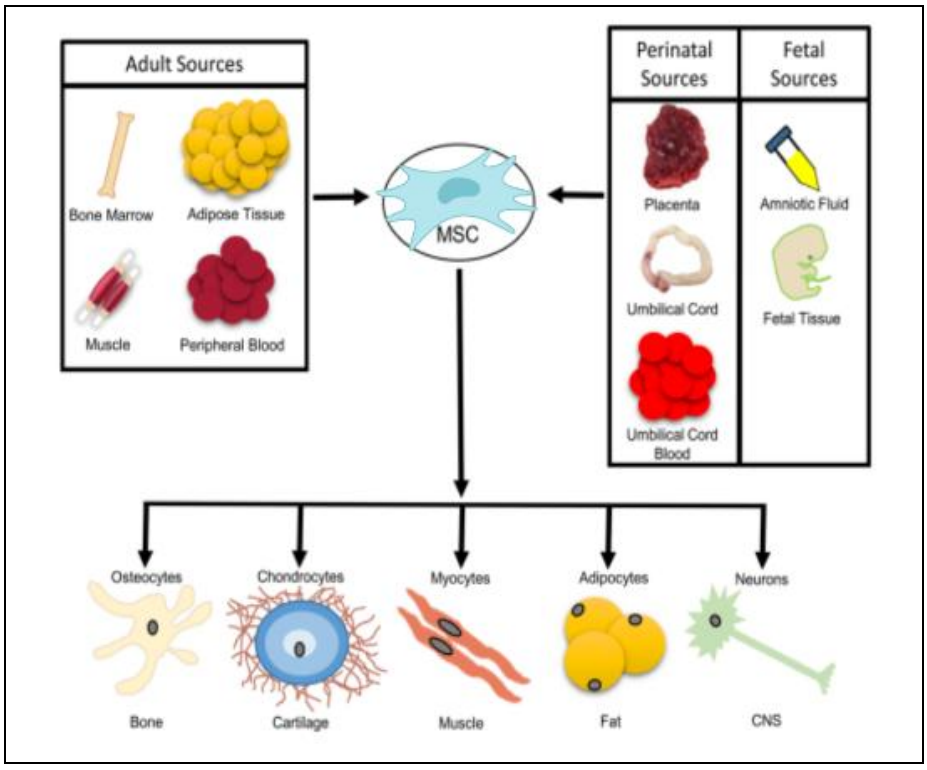

FIG. 1: OUTLETS OF MESENCHYMAL STEM CELLS AND THEIR ROLE IN DISTINCT LINEAGES

TLRs are the first line of defence for the immune system, recognizing chemicals from wounded cells or infections. TLR activation can activate MSCs, which can protect cells from injury/damage. Through the recruitment of neutrophils, MSCs have pro-inflammatory effects in the early stages of inflammation. MIP1 (macrophage inflammatory protein 1), CCL5 (CXC motif ligand 5), CXCL9 (CXC motif ligand 9), and CXCL10 (CXC motif ligand 10) are secreted by pro-inflammatory MSCs, which trigger T cells by attracting additional lymphocytes. There are only minimal amounts of inflammatory markers like TNF and IFN at this stage [7].

In tissue engineering, mesenchymal stem cells are effective based on the earlier research. These MSCs have potential in many diseases, including neuroinflammation, female infertility, and joint disorders. Hence, in this review, we will aim for the efficacy of mesenchymal stem[8].

MSCs in relation to Neuroinflammation: Neuroinflammation is one of the crucial pathological diseases involved in Traumatic Brain Injury (TBI) [9], stroke [10], intracerebral haemorrhage (ICH), and various neurodegenerative diseases [11, 12]. Under optimal circumstances, neuroinflammation is responsible for causing homeostasis and promoting tissue repair. Microglia plays an important role in the beginning and causes neuroinflammatory responses [13]. Similarly, macrophages and microglial cells indicate the plasticity that could polarize towards the classical pathway of M1 or alternative M2 phenotype. M1 microglia (polarized) is characterized by increased pro inflammation cytokines that induce TNF – alpha, IL – 1 beta, and IL – 6 and increase iNOS and CD16 levels. On the other hand, M2 polarized microglia have the potential to exaggerate M2 phenotype markers like Ym – ½, CD – 206, TGF – beta, and Arg – 1. Functionally, M1 microglia disturb neural injury and retard the cellular reactor after CNS disruption, while M2 microglia can protect neurons and leads to recovery and remodelling [14].

Inhibiting M1 microglia polarization and promoting the M2 microglia polarization may be a viable strategy for treating neuroinflammation-related diseases [15, 16]. Several recent studies reveal that administration of MSCs is useful for promoting recovery of function in certain neurological disorders [17, 18]. Previous studies describe that MSCs also reduce the production of inflammatory factors in the microglia by TSG – 6 [19, 20].

The rejuvenation and differential properties of stem cells have been shown as a very good tool for regeneration, restoration, or replacement therapies in several diseases. MSCs have great potential to differentiate into a wide variety of cells. MSCs are adherent cells with a fibroblast-like appearance that can distinguish into bone cells, cartilaginous cells, fat cells, tonocytes, and myocytes [21-26]. MSCs are also responsible for hematopoiesis, including Erythropoiesis, Leucopoesis, thrombopoiesis, and also possess immunomodulatory properties. Many growth substances, chemokines, adhesion molecules, and TLRs [27, 28] mediate the migration of MSCs. They are also successfully used to reverse - graft – versus – host disease in those patients who receive Bone-Marrow transplants [29, 30] and in those identified with the Resistance to Steroids [31-33]. MSCs have the potential to reduce the swelling initiated by regulative T-Cells and decrease the destruction of kidneys and bowel [34-39].

Immunomodulatory Role of MSCs: MSCs are useful as the best tool for cell therapy, particularly for the control of disorders caused due to inflammation based on their immunostimulatory properties, paracrine cell signaling via stimulating characteristics, namely anti-apoptotic, anti-fibrotic and anti-angiogenic [40, 42]. MSCs are also useful in a wide area of the immune system triggered by inflammatory factors produced by activated immune cells, *i.e.*, IFN – gamma, IL – 1 Beta, and TNF – alpha [43-50].

Several studies reveal that MSCs may display immunosuppressive or immunomodulatory properties [43, 51, 52-55]. MSCs also tend to reduce the effects of b inflammatory and protect against the Cytokine Storm. MSCs are placed on the ruptured sites because of hypercytokinemia [56], which switches on the immune system. The movement and activation of mesenchymal stem cells may also bring out several growth and immunomodulatory factors by secreting them. Based on the small protein involved in cell signaling known as cytokines (whether the signal is acute or prolonged inflammation), MSCs begin the immunomodulatory response and heal the ruptured sites and impotent to suppress the continuing prolonged inflammatory signals outcome of cellular fibrosis [57, 58].

How Mesenchymal Stem Cells play its Role in Alzheimer disease: By 2006, the world occurrence of Alzheimer's illness was 26.6 million. By 2050, the occurrence will quadruple, whereby 1 in 85 individuals around the world will be dealing with the illness [59-61]. Frequently suggested medications for dementia remain inhibition of cholinesterase and memantine (Namenda) for long-term use and

are considered toxic. Thus, MSCs are the best alternative. They are thought to have superiorities in substantial resources (for example- umbilical cord in humans, adipose tissues and bone marrow), with a decrease in immunogenicity and atypicality self-renewal behavior [62].

Studies had shown that when Aβ-managed neuronal progenitor tissues (NPCs) co-cultured along with MSCs, they boosted the expression of proliferation marker (Ki-67) considerably, neuronal progenitor markers such as (GFAP, nestin, SOX2), as well as a neuronal marker (HuD) compared with Aβ therapy alone. On top of that, MSC therapy during Aβ-treated NPCs (neural progenitor cells) boosted the articulation of Ngn1 and also β-catenin compared with Aβ treated alone and quantitative analysis revealed that the variety of BrdU, as well as HuD dual positive cells in dentate gyrus, was actually considerably greater in the MSC-treated group compared to after Aβ treatment alone. These show MSCs significantly enhance neurogenesis in hippocampus area and enhance the NPCs differentiation (neuronal progenitor cell) into more mature neurons in AD models by activation of signaling pathway *i.e.,* Wnt pathway [63].

The hMSC (Human mesenchymal stem cell) therapy considerably reduced LPS-induced microglial activation, tumor necrosis factor (TNF)-α, inducible nitric oxide synthase (iNOS) mRNA phrase, and also the creation of NO compared to the LPS-only therapy. MSCs might directly or indirectly control the condition of astrocytes or microglia and rely on TFs signifying paths to readjust the equilibrium of inflammatory cytokines, consisting of each pro-inflammatory and anti-inflammatory cytokines [62, 64]. Nevertheless, the underlying systems of MSC treatment for AD stay uncertain. Neuronal reduction in AD is actually partially compensated through MSC transplantation as well as this might be among the mechanisms for MSC treatment in AD [65].

Mesenchymal Stem Cell Role in Parkinson Disease: Parkinson is a gradual neurodegenerative disease because ofmassive damage of dopaminergic neurons in area nigrostriatal pathway and neuron loss in substantia nigra pars compacta which results in debilitating movement disorders [66]. New treatment for PD using different animal models uncovered unusual neurotoxins [67]. One among these models'is 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model exposed to these neurotoxins that helped to determine the pathophysiological mechanism of PD and currently injured rat exposed to 6-OHDA neurotoxin are most used in PD model [68, 69]. There are 2 properties that discuss the regenerative prospective of MSC's: their multipotentiality and secretome. Based on these findings cell therapy strategies for Parkinson disease mainly focused on the ability of stem cells to differentiate into Dopaminergic neurons producing cells that will replace diseased DA neurons [70].

Mesenchymal Stem Cells in Osteoarthritis: Osteoarthritis is one of the prevalent disorder of joints, which causes discomfort and stiffness of joint movements in an individual. In this, articular cartilage decays and the formation of new bone occurs at the same position. OA is commonly observed and leading cause of physical disability in aged individuals, which makes them incapable of doing physical activities. OA occurs in all the synovial joints of an individual which mainly affects the hips and knee movements as well as it also brings out other disorders like depression and sleeping disorder [71]. OA is differentiated into two categories: 1) Genetic factor and 2) Aging.

Particularly, MSC-based therapeutics has been suggested for osteoarthritis. MSCs were mostly found in a thin layer of connective tissue called periosteum, lungs, milk teeth, tendon, synovial stratum, cancellous bone, adipose tissue, tendon, lung, and manymore tissues(9). OA might be the outcome of MSC population malfunctions, leading to a degeneration of bones [72].

Mesenchymal Stem Cells in Female Infertility: In earlier studies, it has been observed that MSCs play an important role in several diseases, including infertility. Infertility in women impacts the quality of health and well-being of women and their families. Infertility can be caused by female reproductive disorders, which are represented in **Fig. 2.** Several conditions like POF, PCOS, Asherman syndrome, endometriosis and fallopian tube obstruction, primary ovarian insufficiency, polycystic ovary syndrome, endometriosis, and fallopian tube obstruction [73]. Primary ovarian

insufficiency, generally called POF, occurs in women below 40 years, affecting 1% of the total women population in the world [74]. Polycystic ovary syndrome, PCOS, is described by increased level of androgen, irregular menstrual cycle, and tiny pouch-like structure on a single or on the pair of ovaries[75]. During the menstrual cycle, the dense innermost layer formation on the uterus known as endometriosis can cause infertility. Asherman syndrome is an acquired disorder [76,] and fallopian tube obstruction occurs due to the blockage in women's fallopian tube. All these symptoms are the main causes of infertility in women worldwide [77].

MSCs treatment for Neuroinflammation: Macrophages and microglia are immune cells that tend to change their phenotypic expression into anti-inflammatory cytokines and prevent damaged neural tissue. In this type of condition, mainly therapies can be used, which will regulate the immune system after Brain ischemia; that is, transplantation of MSCs is getting more success. In earlier research, it has been observed that MSCs are capable of regulating immune response and help information of astrocytes, maturation of nerve tissues, formation of oligodendrocytes, and angiogenesis. Also, damaged cells can be replaced by the paracrine effect, but its release in the environment extracellular vesicles (EV), plays a crucial role. EVs are membrane structures having essential biomolecules such as proteins, lipids, and nucleic acids. Also, they have the potential to explicit the autologous properties as the cells have (from where they are obtained). Therefore, EVs have a decreased immune responseability and cannot blockage the vessel, and have the potential to cross the Blood-Brain Barrier, or we can say BBB. Some studies reveal that MSCs and EVs have immunosuppressive and prevent neural cell death; however, they can stimulate the development of nerve tissues, angiogenesis, and so on. For illustration, the figure is given in **Fig. 2.**

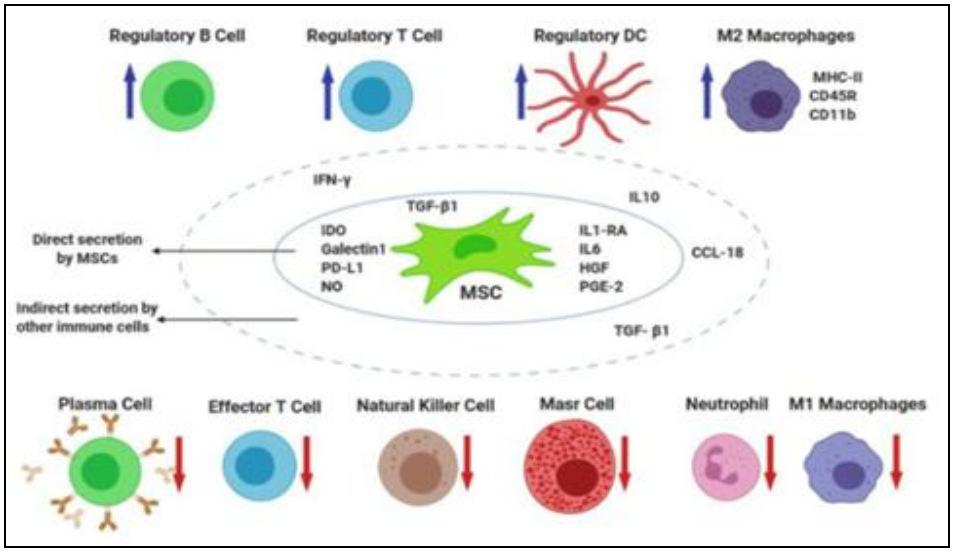

FIG. 2: EFFECTS OF MSCs ON DIFFERENT IMMUNE CELLS

Alzheimer disease and Inflammation: Alzheimer's disease occurs due to Aβ plaques and intracellular NFTs. Microglia and Astrocytes play a critical role in neuroinflammation [74]. It is observed that microglia and β-amyloid plaques in pathogenesis or progression from the neuroimaging analyses in AD of transgenic rodent models, post-mortem human brain. Microglia is recognized for its anti-inflammatory effects and pro-inflammatory [75]. Additionally, Aβ can trigger microglia to produce cytokines and neurotoxins, thus promoting neurodegeneration [76]. Astrocytes are the most abundant kind of glial cells in the main nerves (CNS) and have a lot of operations, consisting of preservation of ionic stabilization, blood-brain obstacle (BBB), and involvement in synaptogenesis, neurogenesis and also synaptic transmission. Astrogliosis happens in AD, and also the level of astrogliosis changes is connected with cognitive problems. Astrocytes reveal a number of receptors for chemokines and also inflammatory cytokines consisting of those like IL-1β and also TNF-α [77].

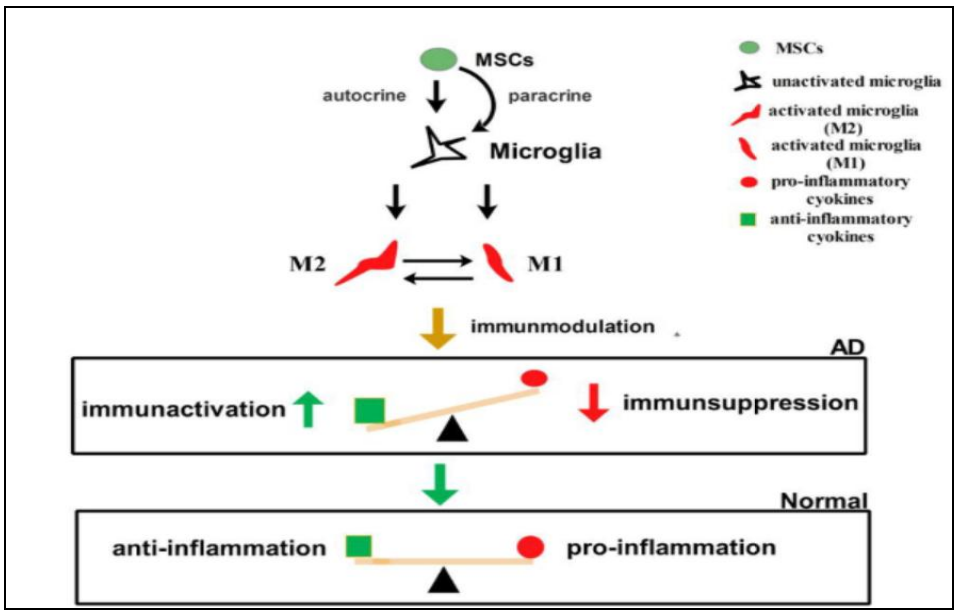

FIG. 3: IMPACT OF MSC-IMMUNOMODULATED MICROGLIA ON AD PROGRESSION. MSCs INFLUENCE THE ACTIVITY STATE OF MICROGLIA, M1(CLASSICALLY ACTIVATED) OR M2 (ALTERNATIVELY ACTIVATED), IN PARACRINE OR AUTOCRINE MANNERS, AND THEN IMMUNOMODULATE THE HOMEOSTASIS OF NEUROINFLAMMATION FOR A RESTORE TO THE NORMAL HEALTHY CONDITION

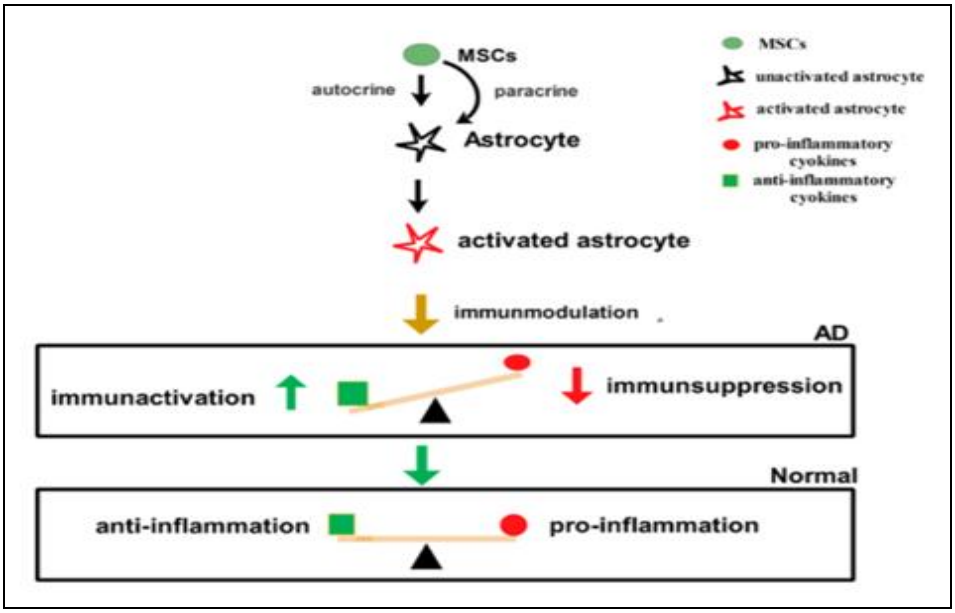

FIG. 4: EFFECT OF MSC-IMMUNOMODULATED ASTROCYTES ON AD PROGRESSION. MSCs AFFECT THE ACTIVITY STATE OF ASTROCYTES BY AUTOCRINE OR PARACRINE MANNERS, AND THE ACTIVATED ASTROCYTES IMMUNOMODULATE THE HOMEOSTASIS OF NEUROINFLAMMATION AND FACILITATE A RETURN TO THE NORMAL HEALTHY CONDITION

MSC Therapy for AD: Microglia-mediated Neuroinflammation: MSCs have greater potential for AD therapy because of no immune rejection. Mechanisms of MSC therapy for AD require further exploration. MSCs have been transplanted into various AD models, and patients with AD show us the immune-modulatory role in AD development by microglia [78]. Systemic replacement of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) into APP/PS1 transgenic mice shows a reduction in the level of interferon-γ (a pro-inflammatory cytokine), increased the levels of IL-10 and transforming growth factor-β1 (anti-inflammatory cytokines) in peripheral plasma and reduce Aβ plaque deposition as well as soluble Aβ which may be related to activation of microglia [79] **Fig. 4**. MSC therapy promote an increase in IL-4, which induce

microglia to produce insulin-like growth factor (IGF)-1 [80]. Reduce Aβ toxicity and boost Aβ phagocytosis [81].

MSC transplanted in the AD model triggered microglia to become activated and covert into an amoeboid shape and reach the area of inflammation. Activated microglia has two phenotypes: M1 (classical activated) and M2 (alternatively activated) [82]. M1 microglia usually produces massive pro-inflammatory cytokines inducing IL-1β, IL-12, TNF-α, and iNOS, which worsens the CNS damage [83, 84]. M2 microglia respond to IL-4, IL-10, IL-13 and TGF-β, which have an anti-inflammatory impact on AD [85]. Interestingly, transplanted MSC decreased Aβ deposition and improved neurological function [86, 71]. By anti-inflammatory cytokines are considered to favour AD improvement [87]. It is seen that activated cytokines can switch between M1 and M2 phenotype by a dynamic process with importance [88]. A mechanism can be of MSC-based therapy in AD that MSCs regulate neuroinflammation by microglia activation. This will reduce pathological features such as tau hyperphosphorylation and Aβ deposits, and save the spatial learning and memory deficits **Fig. 5.**

MSC Therapy for AD: Astrocyte-mediated Neuroinflammation: Studies in APP/PS1 transgenic mice revealed that hypoxic MSC-derived exosomes might efficiently decrease the inside build-up of synaptic protein expression in the brain cells of these mice. Additionally, therapy with exosomes coming from hypoxic MSC reduced activation of glial tissues and degrees of inflammation throughSTAT3 and NF-kB pathways. Exosomes coming from hypoxia-preconditioned MSCs efficiently enhanced the level of miR-21 in the brains of AD mice, which avoided the pathologic conditions in AD mice [89]. Astrocytes make up a particular tissue kind along with a star-shaped morphology resembling inactivated microglia surrounded by close-by neurons and capillary [90] and have lots of essential features consisting of metabolic impacts as well as modulatory impacts on the neuronal microenvironment under physiological conditions [91]. Nonetheless, many triggered astrocytes hasbeen found adjacent to Aβ plaques, suggesting an interaction between activated astrocytes and AD development [92]. MSCs might participate in a restorative function in AD by reducing astrocytes' activation. Furthermore, when MSCs are put on the microenvironment of injured cells, they can easily create different elements like TGF-β as well as IGF-1 that trigger the activation of astrocytes. Consequently, the triggered astrocytes can easily clear Aβ plaque deposition as well as which likewise might trick TGF-β [93] as well as IGF-1 [94] as neuroprotective elements. Nevertheless, the activation of astrocytes has \both advantages and disadvantages. Extreme activation of astrocytes can easily result in astrogliosis colocalized along with amyloid plaques in AD [95] or even glial mark development after CNS damages [96-97].

Wnt Signalling in Alzheimer's disease: Microglia governs the inherent defense inflammation to prevent the brain and helps in improving the performance of CNS [98, 99]. Neuroinflammation has been established as the central pathophysiological pathway of multiple neurodegenerative disorders and microglia are important for neuroinflammation throughout the brain [100-102]. Microglia has a double impact on the prevalence of Alzheimer's disorder [103].

Microglia destroy amyloid-beta (Aβ) to prevent it from forming. They discharge inflammatory and pro-inflammatory factors that contribute to neuroinflammation and the proliferation of tau NFTs and amyloid plaques and pathology [104]. The signal transduction pathway called Wnt signaling pathway acts as a vital factor in determining cell lineage and activity. Both pathological tau phosphorylation and synaptic failure in AD are caused by Wnt pathway dysregulation [105]. The regulatory role of Wnt signalling on microglial inflammation has also been verified in recent studies [106-110].

Wnt signalling is involved in the improvement, renewable and pro tumor etiology of entirely important organs of the body. Wnt signals in the brain helps in vascular healing and the formation of the blood-brain barrier and communicate with microglial neuroinflammation [111]. Both the canonical and non-canonical pathways as well as their cascade components, help compensate Wnt signals [112, 113] **Fig. 5.** High levels of CR3 namely CD68, IBA1, CD11b and CD33 expression shows

the pro-inflammatory activity of altered microglia due to stimulation of Wnt canonical pathway. Yet, as per the existing research, ifWnt signalling has a significant impact on microglial devour is uncertain [113, 114].

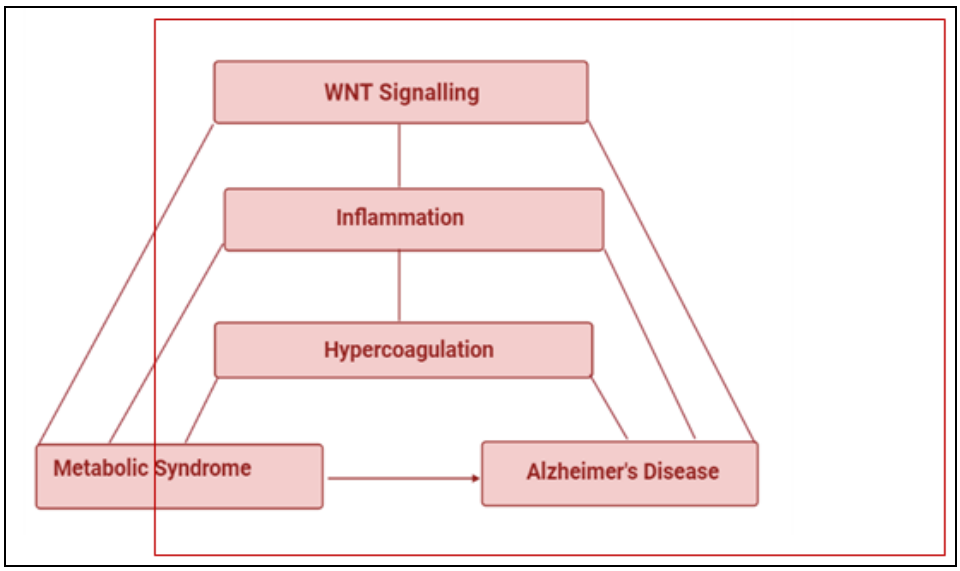

FIG. 5: ROLE OF WNT SIGNALLING IN ALZHEIMER'S DISEASE

Even though microglia are not constitutive components of the CNS, we have demonstrated that they are very closely linked to NPCs, neurons, and other glial cells. Glia consisting of small cells are considered more than immune cells in the CNS as immunological executors. It also impacts neuronal renewal through their interactions with nerve cells, myelinating cells of CNS called oligodendrocytes and astrocytic glial cells, as the importance of Wnt pathways in tissue regeneration has been generally recognized. Microglia plays an important role when cellular aging results in neurodegenerative disorders as these glial cells alter themselves into active form and oppose epidemiological changes of these disorders. Also, it triggers neurodegeneration by inflammatory and immune response [105].

Therapeutic use of MSCs in Parkinson: Secretome consists of a group of paracrine factors mainly formed by cytokines that modify the immune response or the functioning example interleukin-6 (IL-6), prostaglandin E2 (PGE2), and growth factor-beta (TGF-β) [115, 116]. These cytokines inhibit the cytotoxic T lymphocyte proliferation cytokines and stimulate the proliferation of regulatory T lymphocyte [117]. But also, this neurotropic or neuroprotective activity on resident progenitor cells, hence inducing neurogenesis /oligodendrogenesis or anti-apoptotic effects on neuron or glia cells, neurite outgrowth [118] and angiogenesis [119]. Therefore, secretome can help in limiting the process of neuroinflammation and can reverse the damage caused by PD.

Additional therapeutical significance of the ability of MSC to move to the wounded tissue and inflammation is due to signals generated by different factors that are released at these sites [115]. So far, little is known about MSC action in therapeutic mechanisms in these parkinsonian models. But many studies on the therapeutic potential of these paracrine factors work on the hypothesis that nigrostriatal degeneration is done by inflammation. The MSC therapeutic effect could provide some anti-inflammatory mechanism by secretome. For this study, in-vitro dopaminergic producing mesencephalic neurons and mouse microglia are activated by lipopolysaccharides (LPS) were co-culture with human bmMSC; the result shows a remarkable decrease in microglia activation and death of neurons also the amount of pro-inflammatory cytokines in the medium also decrease and show more neurons producing dopamine as compared to control group [120]. This result suggests that MSC role as a potential therapeutic in treating PD is based on immuno-modulation and trans differentiative capacity and stimulates proliferation and endogenous stem-like progenitor cells differentiation found in most tissues, and decreases inflammatory and immune

reactions [121]. Therefore, microenvironment changes in the tissue may be more important than transdifferentiation in effecting tissue repair [122, 123, 124]. MSC can also help by decreasing the alpha-synuclein, which regulates synaptic vesicle trafficking and subsequent neurotransmitter release, by increasing the autophagic process to reduce the accumulation of alpha-synuclein in PD patients [125,126]. When MSC was co-cultured along with neuronal cells and MPP+ (which is an active form of MPTP toxin), alpha-synuclein decreased, and LC3-II level increased, expressing a high number of autophagosomes indicating stem cells can be supplied the survival of dopaminergic neurons.

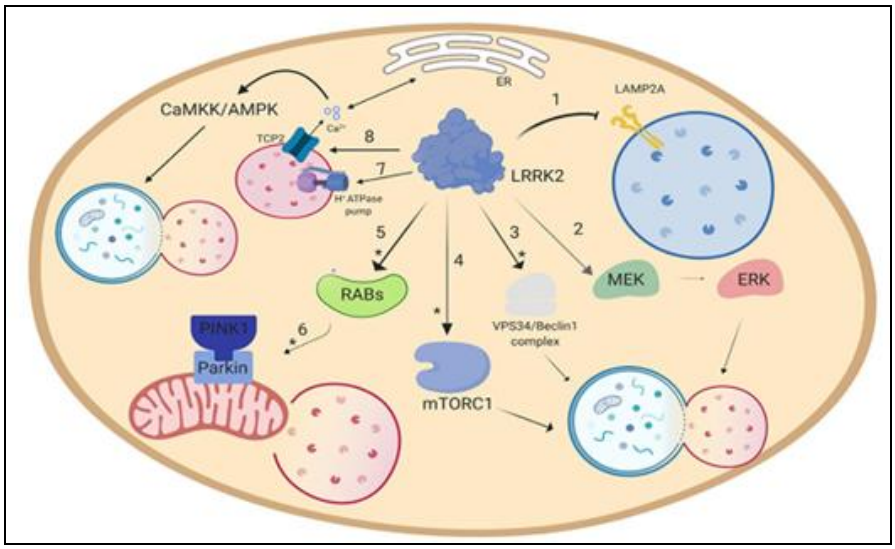

FIG. 6: LRRK2 AS WELL AS ASYN CONTROL OF AUTOPHAGY AT THE PRESYNAPTIC TERMINAL. ADDITIONALLY, PD- CONNECTED PROTEINS ACT UPON EACH SYSTEM, MOST PROBABLY MODULATING A TYPICAL PROCEDURE. FOR INSTANCE, LRRK2, AS WELL AS ASYN, CONTROL AUTOPHAGIC FLUX AS WELL AS LYSOSOMAL TASK, ALONG WITH PD TRIGGERING MUTATIONS IMPAIRING THE PROCEDURE

Role of MSCs in Osteoarthritis Therapy: In recent years, clinical experiments using MSCs to cure human joint cartilage abnormalities have been conducted. It has been suggested that mosaicplasty might be useful to treat knee joint deep zone of cartilage lesions in an individual. This MSC-based therapy's therapeutic advantages contributed to the growth of MSC-based cartilage regeneration techniques. In addition, low, middle, and high-dose intra-articular injections of AD MSCsfor osteoarthritis therapy were studied. It is also found that injecting MSCs into an osteoarthritic knee improved pain and function without generating any side effects, and the renewal of articular cartilage minimized cartilage defects. By injecting joint injection of MSCs has proven to enhance a patient's condition with OA as it relieves the pain of joints and other deteriorating joint disorders, as previously indicated. The potential of MSC exosomes to limit cartilage degradation and subchondral bone disintegration, reduce osteophyte development, and prevent synovial inflammation were among the benefits of intra-articular injection of MSC exosomes for OA therapy [127]. Other MSC distribution technologies include joint injection called intra articular, fibrous scaffolds, fibrin sealant, TECs (tissue-engineered constructs) and Hyaluronic acid hydrogel-based drug delivery systems **Fig. 6.**

MSCs in the Treatment of Female Infertility: MSCs have efficacy in therapeutics due to their ability to differentiate into diverse cell fate and regulate modulation of immune system by regulating immune responses. Also, they have been dividing into stromal, endothelial, and epithelial cells which thickens endometrium and enhance gestation results [128]. When MSCs are kept in various cell culture conditions, theyshould be plastic-adherent. Then, MSCs surface biomarkers CD73, CD90 and CD105n expresses itself 129,130. In earlier research, MSCs played a role in diagnosing infertility by improving ovarian performance. MSC therapy *in-vivo* increases ovarian function and this effect may be intervening *via* signaling paracrine pathways. MSCs associate

with immune cells and have immunomodulatory effects [131]. Moreover, the RAP1/NFkb signaling pathway controls MSC paracrine activity.

In reproductive system illnesses associated with inflammation, the NFkb signalling pathway is extremely active [132]. Such responses appear to be linked to mechanisms that promote renewal and angiogenesis, which may help ovarian function. As these pathways may modulate inflammatory immune responses, heal wounded tissues, and induce stem cell precursors to develop into particular tissue cells, this possible mechanism of MSC activity is of significant concern. Furthermore, miRNAs and exosome transfer provide a special way by which MSCs exert roles via mitochondrial transfer, a crucial factor in many biotic functions in life and illness, including premature ovarian failure [133].

Certain inflammatory cytokines, such as IL-6 and TNF-, can cause MSC skeletal rearrangement and the formation of tunnelling nanotubes (TNT), which allow mitochondria to move from mesenchymal stem cells to neighbouring cells such as AECs (airway epithelial cells), cardiac muscle cells and RGC (retinal ganglion cells). MSC mitochondrial replacement to reproductive organs, including oocytes, has also been observed lately because of inflammation [134].

CONCLUSION: It has been observed that mesenchymal stem cells' immunomodulatory properties help improve individuals' health conditions. MSC can switch cells from basal ganglia and nigrostriatal dopamine system and in many different areas of the brain, will be beneficial for Parkinson's Disease patients. As for secretome, neurotrophic factors and immunomodulatory cytokines lower neuroinflammation and provide an environment for dopaminergic neurons to survive. Also, it may function in cellular treatment or gene for the model of Parkinsonism to increase the longevity of transplanted cells. And astrocytes or even microglia regulated through MSCs might participate in greater than individual functions. In AD, Aβ plaques most probably trigger astrocytes or even microglia. It is feasible that the activation of microglia participates in an essential function in the activation of astrocytes. For this reason, the communication between the activation of microglia and the activation of astroglia might be associated with the pathogenesis of AD.

Likewise, the MSC located treatment for AD has actually complicated settings by modulating the activation of microglia or even astroglia. Wnt pathway can enhance the chances of treatment of AD in future aspects. Since MSCs have a long history of usage in joint healing, using them to treat OA is highly enticing. Animal research has provided far motivation and the reasoning for moving on with human trials.

The effective isolation and cultivation of MSCs from identified and dependable sources might be a future direction. The synthesis of different biomaterials optimizes mesenchymal stem cells' efficacy for reproductive system cells. MSC transport vehicles made of collagen-based drug delivery have also been used to improve stem cell engraftment, cell adhesiveness, and preservation. However, further work is needed to improve this method.

Footnote:

Funding: Funding information is not applicable. No funding was received.

Ethics Statement: This article does not contain any studies with human participants or animals performed by any of the authors.

ACKNOWLEDGMENT: The authors would like to acknowledge the Management of JSS Academy of Higher Education & Research, Mysuru, Karnataka, for supporting the basic research ideas and also for the resources provided.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

REFERENCES:

1. Han Y, Li X, Zhang Y, Han Y, Chang F & Ding J: Mesenchymal Stem Cells for Regenerative Medicine. Cells 2019; 8(8): 886.
2. Chang Z, Zhu H, Zhou X, Zhang Y, Jiang B, Li S, Chen L, Pan X & Feng XL: Mesenchymal Stem Cells in Preclinical Infertility Cytotherapy: A Retrospective Review. Stem Cells International 2021; 1–12.
3. Jiang W & Xu J: Immune modulation by mesenchymal stem cells. Cell proliferation, 53(1), e12712.
4. Rungsiwiwut R, Virutamasen P & Pruksananonda K: Mesenchymal stem cells for restoring endometrial

function: An infertility perspective. Reproductive Medicine and Biology 2021; 20(1): 13–19.
5. Brown C, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, Svinarich D, Dodds R, Govind CK & Chaudhry GR: Mesenchymal stem cells: Cell therapy and regeneration potential. Journal of Tissue Engineering and Regenerative Medicine 2019; 13(9): 1738–1755.
6. Andrzejewska A, Lukomska B & Janowski M: Concise Review: Mesenchymal Stem Cells: From Roots to Boost. Stem Cells (Dayton, Ohio) 2019; 37(7): 855–864.
7. Ling MP, Lee SDS, Farhana A, Alzahrani B & Ali MS: Photoreceptor Therapy: Generation of Neurosphere-like Cells from Human Mesenchymal Stem Cells Expressing Erythropoietin. Sains Malaysiana 2020; 49(1): 113-119.
8. Naji A, Eitoku M, Favier B, Deschaseaux F, Rouas-Freiss N & Suganuma N: Biological functions of mesenchymal stem cells and clinical implications. Cellular and molecular life sciences: CMLS 2019; 76(17): 3323–3348.
9. Cozene B, Sadanandan N, Farooq J, Kingsbury C, Park YJ, Wang ZJ & Borlongan CV: Mesenchymal Stem Cell-Induced Anti-Neuroinflammation Against Traumatic Brain Injury. Cell Transplantation 2021; 30, 09636897211035715.
10. Chen C, Ai Q, Chu S, Zhang Z, Zhou X, Luo P & Chen N: IMM-H004 protects against oxygen-glucose deprivation/reperfusion injury to BV2 microglia partly by modulating CKLF1 involved in microglia polarization. International Immunopharmacology 2019; 70: 69-79.
11. Bacherini D, Maggi L, Sodi A, Vannozzi L, Mazzoni A, Capone M & Liotta F: CD3+ CD4-CD8- Double-Negative Lymphocytes Are Increased In The Aqueous Humour Of Patients Affected By Retinitis Pigmentosa: Their Possible Role In Mediating Inflammation 2022.
12. Antunes MS, Cattelan Souza L, Ladd FVL, Ladd AABL, Moreira AL, Bortolotto VC & Boeira SP: Hesperidin ameliorates anxiety-depressive-like behavior in 6-OHDA model of Parkinson's disease by regulating striatal cytokine and neurotrophic factors levels and dopaminergic innervation loss in the striatum of mice. Molecular Neurobiology 2020; 57(7): 3027-3041.
13. Martínez-Pinilla E, Rico AJ, Rivas-Santisteban R, Lill J, Rod E, Navarro G & Franco R: Expression of GPR55 and either cannabinoid CB1 or CB2 heteroreceptor complexes in the caudate, putamen, and accumbens nuclei of control, parkinsonian, and dyskinetic non-human primates. Brain Structure and Function 2020; 225(7): 2153-2164.
14. Lyu J, Jiang X, Leak RK, Shi Y, Hu X & Chen J: Microglial responses to brain injury and disease: functional diversity and new opportunities. Translational Stroke Research 2021; 12(3): 474-495.
15. Paul R, Nath J, Paul S, Mazumder MK, Phukan BC, Roy R & Borah A: Suggesting 7, 8-dihydroxyflavone as a promising nutraceutical against CNS disorders. Neurochemistry International 2021; 148, 105068.
16. Catorce MN & Gevorkian G: Evaluation of Anti-inflammatory Nutraceuticals in LPS-induced Mouse Neuroinflammation Model: An Update. Current Neuropharmacology 2020; 18(7): 636-654.
17. Kaniowska D, Wenk K, Rademacher P, Weiss R, Fabian C, Schulz I & Jaimes Y: Extracellular Vesicles of Mesenchymal Stromal Cells Can be Taken up by Microglial Cells and Partially Prevent The Stimulation Induced by β-Amyloid. Stem Cell Reviews and Reports 2022; 1-14.
18. Shin JY & Lee PH: Mesenchymal stem cells modulate misfolded α-synuclein in parkinsonian disorders: a multitarget disease-modifying strategy. Stem Cell Research 2020; 47: 101908.
19. Dunbar H, Weiss DJ, Rolandsson Enes S, Laffey JG & English K: The inflammatory lung microenvironment; a key mediator in msc licensing. Cells 2021; 10(11): 2982.
20. Liu Q & Lu D: Mesenchymal stem cells-macrophage crosstalk and the maintenance of inflammatory microenvironment homeostasis. Frontiers in Cell and Developmental Biology 2021; 9: 1628.
21. Song WJ, Li Q, Ryu MO, Nam A, An JH, Jung YC & Youn HY: Canine adipose tissuederived mesenchymal stem cells pre-treated with TNFalpha enhance immunomodulatory effects in inflammatory bowel disease in mice. Research in Veterinary Science 2019; 125: 176-184.
22. An JH, Li Q, Ryu MO, Nam AR, Bhang DH, Jung YC & Youn HY: TSG-6 in extracellular vesicles from canine mesenchymal stem/stromal is a major factor in relieving DSS-induced colitis. PLoS One 2020; 15(2): e0220756.
23. Song W J, Li Q, Ryu MO, Nam A, An J H, Jung YC & Youn HY: Canine adipose tissue-derived mesenchymal stem cells pre-treated with TNF-alpha enhance immunomodulatory effects in inflammatory bowel disease in mice. Research in Veterinary Science 2019; 125: 176-184.
24. Watanabe Y, Tsuchiya A, Seino S, Kawata Y, Kojima Y, Ikarashi S & Terai S: Mesenchymal stem cells and induced bone marrow-derived macrophages synergistically improve liver fibrosis in mice. Stem Cells Translational Medicine 2019; 8(3): 271-284.
25. Zhang B, Yang L, Zeng Z, Feng Y, Wang X, Wu X & He TC: Leptin potentiates BMP9-induced osteogenic differentiation of mesenchymal stem cells through the activation of JAK/STAT signaling. Stem cells and development 2020; 29(8): 498-510.
26. Hu B, Lv X, Chen H, Xue P, Gao B, Wang X & Cao X: Sensory nerves regulate mesenchymal stromal cell lineage commitment by tuning sympathetic tones. The Journal of Clinical Investigation 2020; 130(7): 3483-3498.
27. Zhang Z, Liu J, Zeng Z, Fan J, Huang S, Zhang L & He TC: lncRNA Rmst acts as an important mediator of BMP9-induced osteogenic differentiation of mesenchymal stem cells (MSCs) by antagonizing Notch-targeting microRNAs. Aging (Albany NY) 2019; 11(24): 12476.
28. Ghasemi A, Saeidi J, Azimi-Nejad M & Hashemy SI: Leptin-induced signaling pathways in cancer cell migration and invasion. Cellular Oncology 2019; 42(3): 243-260.
29. Cetin I & Topçul M: Can mesenchymal stem cells be used to treat COVID 19 induced pneumonia. Biomedical Reports 2020; 13(6): 1-1.
30. Zhou Y, Yamamoto Y, Xiao Z & Ochiya T: The immunomodulatory functions of mesenchymal stromal/stem cells mediated via paracrine activity. Journal of clinical medicine 2019; 8(7): 1025.
31. Zoehler B, Fracaro L, Senegaglia AC & Bicalho MDG: Infusion of mesenchymal stem cells to treat graft versus host disease: the role of HLA-G and the impact of its polymorphisms. Stem Cell Reviews and Reports 2020; 16(3): 459-471.
32. Marino L, Castaldi M A, Rosamilio R, Ragni E, Vitolo R, Fulgione C & Selleri C: Mesenchymal stem cells from the Wharton's jelly of the human umbilical cord: biological properties and therapeutic potential. International Journal of Stem Cells 2019; 12(2): 218.

33. Barrett J & Galipeau J: Mesenchymal Stem Cells: From Bench to Bedside and Back. Cell and Gene Therapies 2019; 219-242.
34. Wang S, Zhu R, Li H, Li J, Han Q & Zhao RC: Mesenchymal stem cells and immune disorders: from basic science to clinical transition. Frontiers of Medicine 2019; 13(2): 138-151.
35. Wang S, Zhu R, Li H, Li J, Han Q & Zhao RC: Mesenchymal stem cells and immune disorders: from basic science to clinical transition. Frontiers of medicine, 2019; 13(2): 138-151.
36. Amor IB, Lainas P, Kassir R, Chenaitia H, Dagher I & Gugenheim J: Treatment of complex recurrent fistula-in-ano by surgery combined to autologous bone marrow–derived mesenchymal stroma cells and platelet-rich plasma injection. International Journal of Colorectal Disease 2019; 34(10): 1795-1799.
37. Salmenkari H A N N E, Laitinen A, Forsgård R A, Holappa M, Linden J, Pasanen L & Nystedt J: The use of unlicensed bone marrow–derived platelet lysate–expanded mesenchymal stromal cells in colitis: a pre-clinical study. Cytotherapy 2019; 21(2): 175-188.
38. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall R S & Manson JJ: COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet 2020; 395(10229): 1033-1034.
39. Gundestrup AK, Lynggaard CD, Forner L, Heino TJ, Jakobsen KK, Fischer-Nielsen A & von Buchwald C: Mesenchymal stem cell therapy for osteoradionecrosis of the mandible: a systematic review of preclinical and human studies. Stem Cell Reviews and Reports 2020; 16(6): 1208-1221.
40. Crippa S, Santi L, Bosotti R, Porro G & Bernardo ME: Bone marrow-derived mesenchymal stromal cells: a novel target to optimize hematopoietic stem cell transplantation protocols in hematological malignancies and rare genetic disorders. Journal of Clinical Medicine 2019; 9(1): 2.
41. Mukherjee S, Baidya A & Barik S: New Approaches in Cancer Research: Stem Cell Research, Translational Research, Immunotherapy and Others. In Cancer Diagnostics and Therapeutics 2022; 377-405. Springer Singapore.
42. Farrokhi AS, Zarnani AH & Moazzeni SM: Mesenchymal stem cells induce expansion of regulatory T cells in abortion-prone mice. Reproduction 2021; 161(4): 477-487.
43. de Freitas CL, Polonio CM, Brandão WN, Rossato C, Zanluqui NG, de Oliveira LG & Peron JPS: Human Fallopian Tube–Derived Mesenchymal Stem Cells Inhibit Experimental Autoimmune Encephalomyelitis by Suppressing Th1/Th17 Activation and Migration to Central Nervous System. Stem Cell Reviews and Reports 2021; 1-17.
44. Jia H, He J, Zhao L, Hsu CC, Zhao X, Du Y & Ye H: Combination of stem cell therapy and acupuncture to treat ischemic stroke: a prospective review. Stem Cell Research & Therapy 2022; 13(1): 1-16.
45. Joel M D M, Yuan J, Wang J, Yan Y, Qian H, Zhang X & Mao F: MSC: immunoregulatory effects, roles on neutrophils and evolving clinical potentials. American Journal of Translational Research 2019; 11(6): 3890.
46. Taghavi-Farahabadi M, Mahmoudi M, Rezaei N & Hashemi SM: Wharton's Jelly Mesenchymal Stem cells exosomes and conditioned media increased Neutrophil lifespan and phagocytosis capacity. Immunological Investigations 2021; 50(8): 1042-1057.
47. Guerrero B, Hassouneh F, Delgado E, Casado JG & Tarazona R: Natural killer cells in recurrent miscarriage: An overview. Journal of Reproductive Immunology 2020; 142: 103209.
48. Abbasi B, Shamsasenjan K, Ahmadi M, Beheshti SA & Saleh M: Mesenchymal stem cells and natural killer cells interaction mechanisms and potential clinical applications. Stem Cell Research & Therapy 2022; 13(1): 1-18.
49. Liu X, Zhao Z, Zhao Z, Xu Z, Cao J, Wang B & Suo G: Heterogeneity of mesenchymal stem cells: characterization and application in cell therapy. STE Medicine 2022; 3(1): 109-109.
50. Singer W, Dietz AB, Zeller AD, Gehrking TL, Schmelzer JD, Schmeichel AM & Low PA: Intrathecal administration of autologous mesenchymal stem cells in multiple system atrophy. Neurology 2019; 93(1): 77-87.
51. Canosa S, Mareschi K, Marini E, Carosso AR, Castiglia S, Rustichelli D & Fagioli F: A Novel Xeno-Free Method to Isolate Human Endometrial Mesenchymal Stromal Cells (E-MSCs) in Good Manufacturing Practice (GMP) Conditions. International Journal of Molecular Sciences 2022; 23(4): 1931.
52. Lakota J, Dubrovcakova M & Haider KH: Human Mesenchymal Stem Cells: The Art to Use Them in the Treatment of Previously Untreatable. In Handbook of Stem Cell Therapy Singapore: Springer Singapore 2022; 1-20.
53. Vieira Paladino, F, de Moraes Rodrigues, J, da Silva A & Goldberg AC: The immunomodulatory potential of Wharton's jelly mesenchymal stem/stromal cells. Stem cells international 2019.
54. Chen C, Zhang XR, Ju ZY & He WF: Advances in the research of mechanism and related immunotherapy on the cytokine storm induced by coronavirus disease 2019. Zhonghua shao shang za zhi= Zhonghuashaoshangzazhi= Chinese journal of burns 2020; 36(6): 471-475.
55. Rawat S, Gupta S & Mohanty S: Mesenchymal stem cells modulate the immune system in developing therapeutic interventions. Immune Response Activation and Immunomodulation 2019; 103.
56. Xu AL, Rodriguez LA, Walker III, KP, Mohammadipoor A, KamuchekaR M, Cancio LC & Antebi B: Mesenchymal stem cells reconditioned in their own serum exhibit augmented therapeutic properties in the setting of acute respiratory distress syndrome. Stem Cells Translational Medicine 2019; 8(10): 1092-1106.
57. Dorronsoro A, Lang V, Ferrin I, Fernández-Rueda J, Zabaleta L, Pérez-Ruiz E & Trigueros C: Intracellular role of IL-6 in mesenchymal stromal cell immunosuppression and proliferation. Scientific Reports 2020; 10(1): 1-12.
58. Yoshida S, Miyagawa S, Toyofuku T, Fukushima S, Kawamura T Kawamura A & Sawa Y: Syngeneic mesenchymal stem cells reduce immune rejection after induced pluripotent stem cell-derived allogeneic cardiomyocyte transplantation. Scientific Reports 2020; 10(1): 1-11.
59. HindeyaGebreyesus H and Gebrehiwot Gebremichael T: The Potential Role of Astrocytes in Parkinson's Disease (PD). Medical Sciences (Basel, Switzerland) 2020; 8(1). DOI: 10.3390/medsci8010007
60. Kin K, Yasuhara T, Kameda M & Date I: Animal models for Parkinson's disease research: trends in the 2000s. International Journal of Molecular Sciences 2019; 20(21): 5402.
61. Mustapha M & Taib CNM: MPTP-induced mouse model of Parkinson's disease: A promising direction for therapeutic strategies. Bosnian Journal of Basic Medical Sciences 2021; 21(4): 422.

62. Troshev D, Voronkov D, Pavlova A, Abaimov D, Latanov A, Fedorova T & Berezhnoy D: Time Course of Neurobehavioral Disruptions and Regional Brain Metabolism Changes in the Rotenone Mice Model of Parkinson's Disease. Biomedicines 2022; 10(2): 466.
63. Li J, Liu Y, Zhang Y, Yao B, Li Z, Song W & Huang S: Biophysical and biochemical cues of biomaterials guide mesenchymal stem cell behaviors. Frontiers in Cell and Developmental Biology 2021; 9: 397.
64. Jonas LA, Jain T & Li YM: Functional insight into LOAD-associated microglial response genes. Open Biology 2022; 12(1): 210280.
65. Niu L, Luo SS, Xu Y, Wang Z, Luo D, Yang H, & Wan W: The critical role of the hippocampal NLRP3 inflammasome in social isolation-induced cognitive impairment in male mice Neurobiology of Learning and Memory 2020; 175: 107301.
66. Park JS, Kam TI, Lee S, Park H, Oh Y, Kwon SH, & Lee S: Blocking microglial activation of reactive astrocytes is neuroprotective in models of Alzheimer's disease Acta neuropathologica communications 2021; 9(1): 1-15.
67. Sarlus H & Heneka MT: Microglia in Alzheimer's disease The J of clinical investigation 2017; 127(9): 3240-3249.
68. Mills WA, Woo AM, Jiang S, Martin J, Surendran D, Bergstresser M & Sontheimer H: Astrocyte plasticity in mice ensures continued endfoot coverage of cerebral blood vessels following injury and declines with age. Nature communications 2022; 13(1): 1-15.
69. Fan XL, Zhang Y, Li X & Fu QL: Mechanisms underlying the protective effects of mesenchymal stem cell-based therapy. Cellular and molecular life sciences 2020; 77(14): 2771-2794.
70. Algraittee SJR & Ramasamy R: Characteristics and Functions of Mesenchymal Stem Cells Derived from Nonosteoarthritis and Osteoarthritis Conditions In Handbook of Research on Nano-Drug Delivery and Tissue Engineering: Guide to Strengthening Healthcare Systems. CRC Press 2022; 405-428.
71. Li Y, Yang J, Liu Y, Yan X, Zhang Q, Chen J & Yuan X: Inhibition of mTORC1 in the rat condyle subchondral bone aggravates osteoarthritis induced by the overly forward extension of the mandible. American Journal of Translational Research 2021; 13(1): 270.
72. Zhao YX, Chen SR, Su PP, Huang F H, Shi YC, Shi QY & Lin S: Using Mesenchymal Stem Cells to Treat Female Infertility: An Update on Female Reproductive Diseases Stem cells international 2019; 9071720.
73. Zhang C: The Roles of Different Stem Cells in Premature Ovarian. Failure Current stem cell research & therapy 2020; 15(6): 473–481.
74. Rocha AL, Oliveira F R, Azevedo RC, Silva VA, Peres TM, Candido AL, Gomes KB & Reis FM: Recent advances in the understanding and management of polycystic ovary syndrome F1000Research 8 F1000 Faculty Rev 2019; 565.
75. Dreisler E & Kjer JJ: Asherman's syndrome: current perspectives on diagnosis and management. International Journal of Women's Health 2019; 11: 191–198.
76. Podleśny-Drabiniok A, Marcora E & Goate AM: Microglial phagocytosis: A disease-associated process emerging from Alzheimer's disease genetics. Trends in Neurosciences 2020; 43(12): 965-979.
77. Mora Rodríguez JA, Porchia LM, Camargo F & López-Bayghen E: The use of insulin-like growth factor 1 improved the parameters of the seminogram in a patient with severe oligoasthenoteratozoospermia. SAGE Open Medical Case Reports 2019; 7 2050313X19834154
78. Oncu AE, Ozdemir HU, Orhan HI, Akdeniz BCC, Toprakci A, Aslihak MA & Dinc F: Analytical investigation of long-time diffusion dynamics in a synaptic channel with glial cells. IEEE Communications Letters 2021; 25(11): 3444-3448.
79. Zhao SC, Ma LS, Chu ZH, Xu H, Wu WQ & Liu F: Regulation of microglial activation in stroke. Acta Pharmacologica Sinica 2017; 38(4): 445-458.
80. Zheng ZV & Wong KCG: Microglial activation and polarization after subarachnoid hemorrhage. Neuroimmunology and Neuroinflammation 2019; 6.
81. Dionisio-Santos DA, Olschowka JA & O'Banion MK: Exploiting microglial and peripheral immune cell crosstalk to treat Alzheimer's disease Journal of neuroinflammation 2019; 16(1): 1-13.
82. Tantillo E, Vannini E, Cerri C, Spalletti C, Colistra A, Mazzanti CM & Caleo M: Differential roles of pyramidal and fast-spiking GABAergic neurons in the control of glioma cell proliferation Neurobiology of disease 2020; 141: 104942.
83. Mudò G, Frinchi M, Nuzzo D, Scaduto P, Plescia F, Massenti MF & Grimaldi LM: Anti-inflammatory and cognitive effects of interferon-β1a (IFNβ1a) in a rat model of Alzheimer's disease. Journal of .euroinflammation 2019; 16(1): 1-16.
84. Singh K & Rao A: Probiotics: A potential immunomodulator in COVID-19 infection management. Nutrition Research 2021; 87: 1-12.
85. Saitgareeva AR Bulygin KV Gareev IF Beylerli OA & Akhmadeeva LR: The role of microglia in the development of neurodegeneration. Neurological Sciences 2020; 41: 3609-3615.
86. Ishiuchi N, Nakashima A, Yoshida K, Maeda S, Kanai R, Yamada Y & Masaki T: Hypoxia-preconditioned mesenchymal stem cells prevent renal fibrosis and inflammation in ischemia-reperfusion rats. Stem Cell Research & Therapy 2020; 11(1): 1-15.
87. Yu X Nagai J & Khakh BS: Improved tools to study astrocytes. Nature Reviews Neuroscience 2020; 21(3): 121-138.
88. Yong HY, Rawji KS, Ghorbani S, Xue M & Yong VW: The benefits of neuroinflammation for the repair of the injured central nervous system. Cellular & Molecular Immunology 2019; 16(6): 540-546
89. McQuade A & Blurton-Jones M: Microglia in Alzheimer's disease: exploring how genetics and phenotype influence risk. J of .olecular Biology 2019; 431(9): 1805-1817.
90. He MX, Shi M, Yang T, Yang T and Li J: Chen Mesenchymal stem cells-derived IL6 activates AMPK/mTOR signaling to inhibit the proliferation of reactive astrocytes indused by hypoxic-ischemic brain damage. Exp Neurol 2019; 311: 15–32. https://doiorg/101016/jexpneurol201809006
91. Cui GH, Guo HD, Li H Zhai Y, Gong ZB, Wu J & Liu JR: RVG-modified exosomes derived from mesenchymal stem cells rescue memory deficits by regulating inflammatory responses in a mouse model of Alzheimer's disease. Immunity & Ageing 2019; 16(1): 1-12.
92. Beretta C Nikitidou E Streubel-Gallasch L Ingelsson M Sehlin D & Erlandsson A: Extracellular vesicles from amyloid-β exposed cell cultures induce severe dysfunction in cortical neurons. Scientific reports 2020; 10(1): 1-14.
93. Milà-Alomà M, Salvadó G, Gispert JD, Vilor-Tejedor N, Grau-Rivera O, Sala-Vila A & ALFA: Study Amyloid beta tau synaptic neurodegeneration and glial biomarkers in the preclinical stage of the. Alzheimer's continuum Alzheimer's & Dementia 2020; 16(10): 1358-1371.

94. Echeverri K: The various routes to functional regeneration in the central nervous system. Communications biology 2020; 3(1): 1-4.
95. Chen S, Yang J, Wei Y & Wei X: Epigenetic regulation of macrophages: from homeostasis maintenance to host defense. Cellular & Molecular Immu 2020; 17(1): 36-49.
96. Yeh H & Ikezu T: Transcriptional and epigenetic regulation of microglia in health and disease. Trends in Molecular Medicine 2019; 25(2): 96-111.
97. Baas PW and Qiang L: Tau: it's not what you think. Trends Cell Biol 2019; 29: 452–461 doi: 101016/jtcb201902007
98. Golde TE: Harnessing immunoproteostasis to treat neurodegenerative disorders Neuron 2019; 101(6): 1003-1015.
99. Dressman D & Elyaman W: T Cells: A Growing Universe of Roles in Neurodegenerative Diseases. The Neuroscientist 2021; 10738584211024907
100. Amal H, Gong G, Gjoneska E, Lewis SM, Wishnok JS and Tsai LH: S-nitrosylation of E3 ubiquitin-protein ligase RNF213 alters noncanonical Wnt/Ca+2 signaling in the P301S mouse model of tauopathy. Transl Psychiatry 2019; 9: 44 doi: 101038/s41398-019-0388-7
101. Bellver-Landete V, Bretheau F, Mailhot B, Vallières N, Lessard M and Janelle ME: Microglia are an essential component of the neuroprotective scar that forms after spinal cord injury Nat Commun 2019; 10: 518 doi: 101038/ s41467-019-084460
102. Flores-Hernández E, Velázquez DM, Castañeda-Patlán MC, Fuentes-García G, Fonseca-Camarillo G, Yamamoto-Furusho JK & Robles-Flores M: Canonical and non-canonical Wnt signaling are simultaneously activated by Wnts in colon cancer cells Cellular Signalling 2020; 72: 109636.
103. Reddy YP, Tiwari S, Tomar LK, Desai N & Sharma VK: Fluoride-induced expression of neuroinflammatory markers and neurophysiological regulation in the brain of wistar rat model. Biological Trace Element Research 2021; 199(7): 2621-2626.
104. Cherubini A, Barilani M, Rossi RL, Jalal MMK, Rusconi F, Buono G: FOXP1 circular RNA sustains mesenchymal stem cell identity *via* microRNA inhibition Nucleic Acids Res 2019; 47: 5325–5340 doi: 101093/nar/ gkz199
105. Largo-Barrientos P, Apóstolo N, Creemers E, Callaerts-Vegh Z, Swerts J, Davies C & Verstreken P: Lowering Synaptogyrin-3 expression rescues Tau-induced memory defects and synaptic loss in the presence of microglial activation Neuron 2021; 109(5): 767-777 .
106. Edwards FA: A unifying hypothesis for Alzheimer's disease: from plaques to neurodegeneration. Trends Neurosci 2019; 42: 310–322 doi: 101016/jtins2019 03003
107. Palomer E, Buechler J & Salinas PC: Wnt signaling deregulation in the aging and Alzheimer's brain. Frontiers in Cellular Neuroscience 2019; 227.
108. Estus S, Shaw BC, Devanney N, Katsumata Y, Press EE, and Fardo DW: Evaluation of CD33 as a genetic risk factor for Alzheimer's disease Acta Neuropathol 2019; 138: 187–199 doi: 101007/s00401-019-02000-4
109. Liang C, Mu Y, Tian H, Wang D, Zhang S, Wang H & Di C: MicroRNA-140 silencing represses the incidence of Alzheimer's disease. Neuroscience Letters 2021; 758: 135674.
110. Ru W, Liu X, Bae C, Shi Y, Walikonis R and Mo Chung J: Microglia mediate HIV-1 gp120-Induced synaptic degeneration in spinal pain neural circuits. J Neurosci 2019; 39: 8408–8421 doi: 101523/JNEUROSCI2851-182019
111. Harvey K & Outeiro TF: The role of LRRK2 in cell signalling. Biochemical Society Transactions 2019; 47(1): 197-207.
112. Sakae N, Heckman MG, Vargas ER, Carrasquillo MM, Murray ME and Kasanuki K: Evaluation of associations of Alzheimer's disease risk variants that are highly expressed in microglia with neuropathological outcome measures J Alzheimer's Dis 2019; 70: 659–666 doi: 103233/JAD-190451
113. Gratuze M, Leyns CE, Sauerbeck AD, St-Pierre MK, Xiong M, Kim N & Holtzman DM: Impact of TREM2 R47H variant on tau pathology–induced gliosis and neurodegeneration. The Journal of Clinical Investigation 2020; 130(9): 4954-4968.
114. Benedek G, Abed El, Latif M, Miller K, Rivkin M, Ahmed Ramadhan Lasu AP, Riek L & Levite M: Macrophage migration inhibitory factor in Nodding syndrome. PLoS Neglected Tropical Diseases 2021; 15(10): e0009821.
115. Amal H, Gong G, Gjoneska E, Lewis SM, Wishnok JS and Tsai LH: S-nitrosylation of E3 ubiquitin-protein ligase RNF213 alters noncanonical Wnt/Ca+2 signaling in the P301S mouse model of tauopathy Transl Psychiatry 2019; 9: 44 doi: 101038/s41398-019-0388-7.
116. Bellver-Landete V, Bretheau F, Mailhot B, Vallières N, Lessard M and Janelle ME: Microglia are an essential component of the neuroprotective scar that forms after spinal cord injury Nat Commun 2019; 10: 518 doi: 101038/ s41467-019-084460
117. Wilson DH, Jarman EJ, Mellin RP, Wilson ML, Waddell SH, Tsokkou P & Boulter L: Non-canonical Wnt signalling regulates scarring in biliary disease *via* the planar cell polarity receptors. Nature Communications 2020; 11(1): 1-13.
118. Reddy YP, Tiwari S, Tomar LK, Desai N & Sharma VK: Fluoride-induced expression of neuroinflammatory markers and neurophysiological regulation in the brain of wistar rat model. Biological Trace Element Research 2021; 199(7): 2621-2626.
119. Cherubini A, Barilani M, Rossi RL, Jalal MMK, Rusconi F Buono G: FOXP1 circular RNA sustains mesenchymal stem cell identity via microRNA inhibition Nucleic Acids Res 47 5325–5340 doi: 101093/nar/ gkz199
120. Mangleburg C G Wu T Yalamanchili H K Guo C Hsieh Y C Duong D M & Shulman J M (2020) Integrated analysis of the aging brain transcriptome and proteome in tauopathy Molecular neurodegeneration 2019; 15(1) 1-17.
121. Edwards FA: A unifying hypothesis for Alzheimer's disease: from plaques to neurodegeneration Trends Neurosci 2019; 42: 310–322 doi: 101016/jtins2019 03003
122. Palomer E, Buechler J & Salinas PC: Wnt signaling deregulation in the aging and Alzheimer's brain. Frontiers in Cellular Neuroscience 2019; 227.
123. Estus S, Shaw BC, Devanney N, Katsumata Y, Press EE and Fardo DW: Evaluation of CD33 as a genetic risk factor for Alzheimer's disease Acta Neuropathol 2019; 138: 187–199 doi: 101007/s00401-019-02000-4
124. Pan W, Hu Y, Wang L & Li J: Circ_0003611 acts as a miR-885-5p sponge to aggravate the amyloid-β-induced neuronal injury in Alzheimer's disease. Metabolic Brain Disease 2022; 1-11.
125. Zhou Y, Yamamoto Y, Xiao Z & Ochiya T: The immunomodulatory functions of mesenchymal stromal/stem cells mediated via paracrine activity. Journal of Clinical Medicine 2019; 8(7): 1025.
126. Zhang R, Ma J, Han J, Zhang W & Ma J: Mesenchymal stem cell related therapies for cartilage lesions and osteoarthritis. AJTR 2019; 11(10): 6275–6289.

127. Rungsiwiwut R, Virutamasen P & Pruksananonda K: Mesenchymal stem cells for restoring endometrial function: An infertility perspective. Reproductive Medicine and Biology 2020; 20(1): 13–19.
128. Yoon SY: Mesenchymal stem cells for restoration of ovarian function. Clinical and Experimental Reproductive Medicine 2019; 46(1): 1–7.
129. Harrell CR, Fellabaum C, Jovicic N, Djonov V, Arsenijevic N & Volarevic V: Molecular Mechanisms Responsible for Therapeutic Potential of Mesenchymal Stem Cell-Derived Secretome Cells 2019; 8(5): 467.
130. Ling L, Feng X, Wei T, Wang Y, Wang Y, Wang Z, Tang D, Luo Y & Xiong Z: Human amnion-derived mesenchymal stem cell (hAD-MSC) transplantation improves ovarian function in rats with premature ovarian insufficiency (POI) at least partly through a paracrine mechanism. Stem cell Res & Therapy 2019; 10(1): 46.
131. Xie Q, Xiong X, Xiao N, He K, Chen M, Peng J, Su X, Mei H, Dai Y, Wei D, Lin G & Cheng L: Mesenchymal Stem Cells Alleviate DHEA-Induced Polycystic Ovary Syndrome (PCOS) by Inhibiting Inflammation in Mice Stem cells international 2019; 9782373
132. Sheng X, Yang Y, Zhou J, Yan G, Liu M, Xu L & Sun H: Mitochondrial transfer from aged adipose-derived stem cells does not improve the quality of aged oocytes in C57BL/6 mice. Molecular Reproduction and Development 2019; 86(5): 516-529.
133. Court AC, Le-Gatt A, Luz-Crawford P, Parra E, Aliaga-Tobar V, Bátiz LF, Contreras RA, Ortúzar MI, Kurte M, Elizondo-Vega R, Maracaja-Coutinho V, Pino-Lagos K, Figueroa FE & Khoury M: Mitochondrial transfer from MSCs to T cells induces Treg differentiation and restricts inflammatory response. EMBO Reports 2020; 21(2): 48052.

How to cite this article:
Shreshtha S, Verma R, Shubham, Gopenath TS and Basalingappa KM: Mesenchymal stem cells (MSCs) as potential sources of treatment of neurodegeneration disease: a strategic review. Int J Pharm Sci & Res 2022; 13(11): 4254-68. doi: 10.13040/IJPSR.0975-8232.13(11).4254-68.