Review article

Stem Cell Conditioned Medium as a Novel Treatment for Neuroinflamation Diseases

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Abstract:

Inflammation is a most important factor that mentioned as causes of many neurodegeneration disease like Parkinson, Alzheimer and ALS. Neuroinflammation is poorly understood like neuroinflamation in Alzheimer and Parkinson. Studies showed that even chronic peripheral inflammation that observe in many diseases like arthritis can cause neurodegeneration and dementia in some cases. The neuroinflammation in many dementia diseases are local and information is limited about it. One of the most important treatments for dementia diseases like Alzheimer is the use of anti-inflammatory drugs like NSAIDS but unfortunately they have poor therapeutic effects on neuroinflammation. Recent studies investigated that conditioned medium extracted from mesenchymal stem cells have neuromodulator effects even could prevent neurodegeneration in some cases. In this study we review effects of mesenchymal stem cell conditioned medium in different central nervous system (CNS) disease associated with neuroinflammation.

Keywords: Neuroinflammation, Stem cell, Conditioned Medium, Neurodegenerative disease.

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Introduction:

Neuroinflammation includes physiological and cellular responses of the nervous system to damage, infection or neurodegenerative diseases(1). Actually neuroinflammation is a complex response involving the activation of glia, release of inflammatory cytokines and chemokines, and generation of reactive oxygen and nitrogen species(2). Microglia is the innate immune system of the central nervous system and are key cellular mediators of neuroinflammatory processesSome chronic/remitting neurological diseases, such as multiple sclerosis, have long been recognized as inflammatory, the term neuroinflammation has come to denote chronic, CNS-specific, inflammation-like glial responses that do not reproduce the classic characteristics of inflammation in the periphery but that may engender neurodegenerative events; including plaque formation, dystrophic neurite growth, and excessive tau phosphorylation(3). Also many viral infection could induce neuroinflammation and neurodegeneration in CNS. A virus can enter the CNS through two distinct, including hematogenous dissemination which the virus gains access to the brain by BBB and neuronal retrograde dissemination (4, 5). Viral infections are associated with highly secreted cytokines, cholesterol increase, elevations of lipopolysaccharide (LPS) concentration, insulin resistance and testosterone deficiency(6), which are all involved in inflammation of the CNS. Chronic low grade inflammation with changes in brain structure that could precipitate neurodegenerative changes associated with Alzheimer's disease and other dementias. For example, neuronal loss is a common feature of major depression and dementia(7).Actually Oxidative stress and chronic neuroinflammation are key pathologic factors in brain aging and neurodegenerative diseases, such as Alzheimer , ALS and Parkinson's diseases. As physiological signaling molecules, reactive oxygen species (ROS) play important roles in many biological processes, but increasing amount of ROS can activate microglia and astrocyte in brain and release inflammatory factors in brain and induce neurodegeneration in CNS (8). There are no specific drugs available to repair loss of neurons, induce neuroregeneration and prevent further neurodegeneration in Alzheimer,Parkinson , ALS and MS patients(9). Current drugs are effective only in reducing the severity of symptoms by limiting the extent of neuroinflammation in these patients(10). Nonsteroidal anti-inflammatory drugs (NSAIDs) show neuroprotective and antioxidant effects, inhibit free radicals production, scavenge free radicals and inhibit nuclear factor-kappa B (NF-kB) and interleukins activation in the CNS(10, 11). But as mentioned NSAIDs can not to induce neuroregeneration and also prevent to neurodegeneration.They just could slow down progress of neuroinflammations in these patients(10). For these reason nowadays researcher are finding a way to stop neuroinflammation in CNS. In among of research, studies showed that conditioned medium extracted from stem cells have anti-inflammatory effect (12-14). Actually stem cell release neuromodulator compounds to their environment that could be use for

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healing of inflammation. We gathered valuable data about effects of stem cell conditioned medium in all of neuroinflammation associated disease to discuss about the advantage and disadvantages of stem cell conditioned medium use in neuroinflammation.

1- Therapeutic effects of Stem cell conditioned medium:

Stem cell therapy are used widely in many disease models (15, 16). There are several problems determined by the long-term use of stem cell–based therapies, including improvements in the survival, engraftment, proliferation, and regeneration of stem cells(17). Recent studies have shown that the majority of donor cell death occurs in the first hours to days after transplantation(18). Also stem cells therapy cannot provide an immediate treatment because of the long waiting time for cell preparation and proliferation (19, 20). As well as certain studies have suggested that the transplantation of stem cells into normal tissues may cause tumor formation (21, 22). Many number of studies have suggested that the principal beneficial effects of stem cells especially Mesenchymal stem cells are likely mediated via paracrine mechanisms rather than replication or differentiation (23, 24). The use of secretome Conditioned medium (CM) has several advantages compared to the use of stem cells, as CM can be manufactured, freeze-dried, packaged, and transported more easily. Moreover, as it is devoid of cells; there is no need to match the donor and the recipient to avoid rejection problems(25). Also CM from Mesenchymal stem cells contains various cytokines, growth factors and microRNAs, which has important roles in modulating the inflammation and can be used instead of stem cell therapy in some cases(26). Neurotrophic factors in CM could access affected neurons in CNS by either directly crossing the blood brain barrier or through the retrograde transport mechanism in CNS(27). Stem cells conditioned medium exert immuneomodulatory functions, including inhibition of microglia and astrocyte function. Mesenchymal stromal cells (MSCs) respond to the inflammatory environment by enhancing expression of immunosuppressive factors thereby influencing target cells through paracrine mechanisms(28). Conditioned medium of MSCs contain of signalling molecules such as TGF-β ,IL-10, CCL9, IFN-α, IFN-β, nitric oxide (NO), VEGF, FGF, HGF, PDGF and membrane-bound vesicles, including microvesicles and exosomes that can be used as anti-inflammatiory substance and even regeneration of tissue (29-32).

2- Stem cell Conditioned medium effects in Alzheimer:

Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterized by a decline in cognitive abilities and the appearance of β-amyloid plaques in the brain. Although the cause of Alzheimer disease is not understood clearly, activated microglia and releasing many pro inflammatory cytokines have the most important role of neuroinflammation and neurodegeneration in Alzheimer disease(33-35).Studies showed that conditioned medium from various stem cells have a lot of neurotrophic factors(36). Studies showed

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that brain derived neurotrophic factor (BDNF) and hepatic growth factor (HGF) extracted from CM supports neuronal survival and plasticity and is involved in learning and memory formation(37-39). Also BDNF inhibits microglial activation and promotes axonal regeneration(38). Matrix metalloproteinase-9 (MMP-9) in CM from the stem cells of human exfoliated deciduous teeth reduces the level of pathogenic Aβ oligomers in AD mice and restores synaptic and cognitive deficits in these mice (40), and also growth factor-β (TGF-β) modulates microglial activation in these CM and could attenuate neuroinflammation in AD model in mice (40). In another study indicated that adipose-derived stem cell of CM can improve antidepression-related behaviors in AD model in mice. This may extend usage of CM to not only regenerative medicine but psychological illness(41). Microglia play a crucial role in disease pathogenesis during neurodegenerative diseases such as Alzheimer's disease(42). M1 phenotype of microglia exerts toxic effects by secreting proinflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-1β, IL-6, and nitric oxide (NO) and plays a role as a major component of the neuroinflammatory response but M2 phenotype is involved in the maintenance of CNS homeostasis, phagocytizing apoptotic bodies, releasing neurotrophic factors, and reducing proinflammatory cytokines (43). Mesenchymal stem cell conditioned medium can modulate microglial function via TGF-β (44) and induce microglia into M2 phenotype and promoted Aβ-phagocytosis so reduce Aβ plaques in AD mouse models(45).

3- Stem cell Conditioned medium effects in Amyotrophic Lateral Sclerosis (ALS):

Amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease, known as motor neuron disease is defined by progressive loss of motor neurons, resulting in paralysis and death (46, 47). Oxidative stress and motor neuron excitotoxic death have been linked to neuroinflammatory responses, like elevations of pro-inflammatory cytokines in the CNS(48, 49), astrocyte (50) and microglia activation(51).These pathogenic properties are thought to play important roles in motor neuron death and ALS progression. In another study showed that lifespan in ALS model of mice following adipose stem cell conditioned medium (ASC-CM) administration was increased and correlated with increased in numbers of motor neuron survival in the spinal cord lumbar area(52). Also ASC-CM could prevent early disease pathology, which supports its use in familial ALS. These data emphasize that early identification in at-risk populations for developing ALS is more effectiveness (53). MSC secrete a variety of cytokines and growth factors(54). Evidence from preclinical studies suggested the neuroprotective effects of MSCs seem to be mainly based on anti-inflammatory and immunomodulatory activities of these cells (54). MSC have already been used in ALS patients in a clinical phase I - trial and few adverse effects have been observed which is in favor of further clinical evaluation of this approach and it's more safe if we use MSC-CM instead of MSC as we mentioned CM is

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effectiveness as MSC because of neuromodulatory and neuroprotective composition with less adverse effects (55, 56). Also Data indicate that MSC-CM exerts a protective role against in vitro induced apoptosis in different cell types (primary motor neurons and astrocytes) and maintains its protective potential in motor neurons. This function may involve the activation of both MAPK/Erk1/2 and PI3K/Akt pathways. The regulation of astrocytic neurotrophic factor expression and secretion contributes to MSC-mediated neuroprotection in ALS(57)**.**

4- Stem cell Conditioned medium effects in Parkinson disease:

Parkinson's disease (PD) is one of the most famous of neurodegenerative disease. This disease is hallmark with loss of dopaminergic neurons in specific region of midbrain that named substantia nigra pars compacta (SNpc). Motor and psychological disorders of PD are caused by dopamine loss of corpus striatum as the result of nigrostriatal pathway degeneration (58-61). Chronic neuroinflammation is one of the hallmarks of PD pathophysiology. Post-mortem analyses of human PD patients and experimental animal studies indicate that activation of glial cells and increases in pro-inflammatory factor levels are in the PD brain(61).Studies showed that CM could improve PD symptoms. For example in one study ASC-CM protects from dopaminergic neurons in PD. Neuroprotection by ASC-CM was associated with stimulation of BDNF and NT3 genes expression and tyrosine hydroxylase positive (TH+) neurons preservation(62). BDNF is a neurothrophic factor that is very important for growth and survival of neurons of the SNpc. Reduced expression of BDNF within the SNpc has been shown to cause the loss of dopaminergic neurons in PD(63). Also in another study conditioned medium taken from epithelial cells of choroid plexus (CPECs-CM) was capable of inducing neuronal and dopaminergic differentiation of umbilical cord mesenchymal stem Cells (UCMSCs). Actually CM factors provides signaling molecules for proliferation of neural progenitor cells required for neurogenesis in dopaminergic neurons(64). In a rat model for PD, the efficacy of neurotrophic factors form stem cells was superior to that of mesenchymal stem cells in terms of behavioral, biochemical, and histological indices. Also surviving cells migrated toward the lesion in SNpc is more in the presence of CM of MSC and had the most significant effect at the end of the migration trail. Stromal cell-derived factor-1alpha (SDF-1alpha) is also reported as one of chemokines released from MSCs. SDF-1alpha in CM of MSC increased DA release and suppressed cell death by decline of 6-hydroxydopamine (6-OHDA). 6-OHDA is a neurotoxic compound that destroy dopamine and noradrenaline and recently been found to be formed endogenously in patients suffering from PD(65). So MSC secretome has neuroprotective effects by SDF-1 and 6-OHDA and also many neurotrophic factors in CM that inhibit degeneration of DA neurons in PD models.

5- Stem cell Conditioned medium effects in Multiple Sclerosis:

Multiple sclerosis (MS) is a long-term and autoimmune disease that attacks the central

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nervous system, affecting the brain, spinal cord, and optic nerves(66). MS is characterized by neuroinflamation, demyelination and axonal loss. In one study showed single i.v. injection of stem cell of human exfoliated deciduous conditioned medium (SHED-CM) reduced the severity of encephalomyelitis (EAE) that is a model for MS by suppressing the neuroinflammation, demyelination, and axonal injury associated with this disease(67). Also Analysis of the spinal cord of treated mice with SHED-CM showed that induced a shift in the macrophage phenotype from an M1 proinflammatory phenotype to an M2 anti-inflammatory phenotype, as well as suppressed the expression of proinflammatory mediators(67). In a clinical study, both bone marrow mesenchymal stem cell conditioned medium (BMSC-CM) is safe with relative efficacy in stabilizing the disease and reversing symptoms(68). In another study investigated indoleamine 2,3-dioxygenase, IL-6, PGE2, LIF, and HGF, contribute to the immunosuppressive effects of MSCs(69, 70). HGF, in particular, is thought to be the critical factor in human BMMSC-CM that promotes tissue regeneration and drives the anti-proliferative effect on T cells(71). The effects of both HGF in CM are mediated through the tyrosine kinase receptor cMet and mediate enhanced myelin repair as well as immunomodulation(71). These studies raise the possibility that the HGF/cMet pathway may provide novel therapeutic opportunities for the treatment of MS. In another study also showed that the immunomodulating activity by conditioned medium from ASC-CM that could be considered as a promising tool in MS therapy(72). Actually analysis revealed that MSCs express a number of proteins that modulate immune responses, cell migration, cell proliferation, and CNS repairing, but the exact composition of CM is more complicated than initially envisioned and remains to be elucidated(73). Also in another study IL-37 in MSCs-CM decrease EAE and modulates the balance between pro- and anti-inflammatory cytokines, that IL-37 could be a promising tool in MS management(74). Actually there is a significant down-regulation of its expression in spinal cord from mice with EAE, which was restored by MSCs-CM treatment. Also a significant reduction of the pro-inflammatory cytokines observed in mice with EAE that treated with MSCs-CM(74).

Conclusion:

This review collect many studies about the benefits of CM administration in neuroinflammatory and neurodegenerative diseases (Fig.1.) . CM has a lot of anti-inflammatory cytokines and it has been proven as an inflammatory modulation composition. Despite a great number of promising results in stem cell-CM , and the urgency of having an efficient treatment to patients who suffer from neurodegenerative diseases, we caution on the use of CM in clinical trials, because there remains a lack of understanding of the effect of these composition on brain tissue and more studies are necessary in clinical trials on neurological diseases, to make sure that these CM do not have the potential to cause severe adverse effects in humans and also we need to try CM of different stem cells to

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achieve for maximum effect of healing in neurodegenerative diseases.

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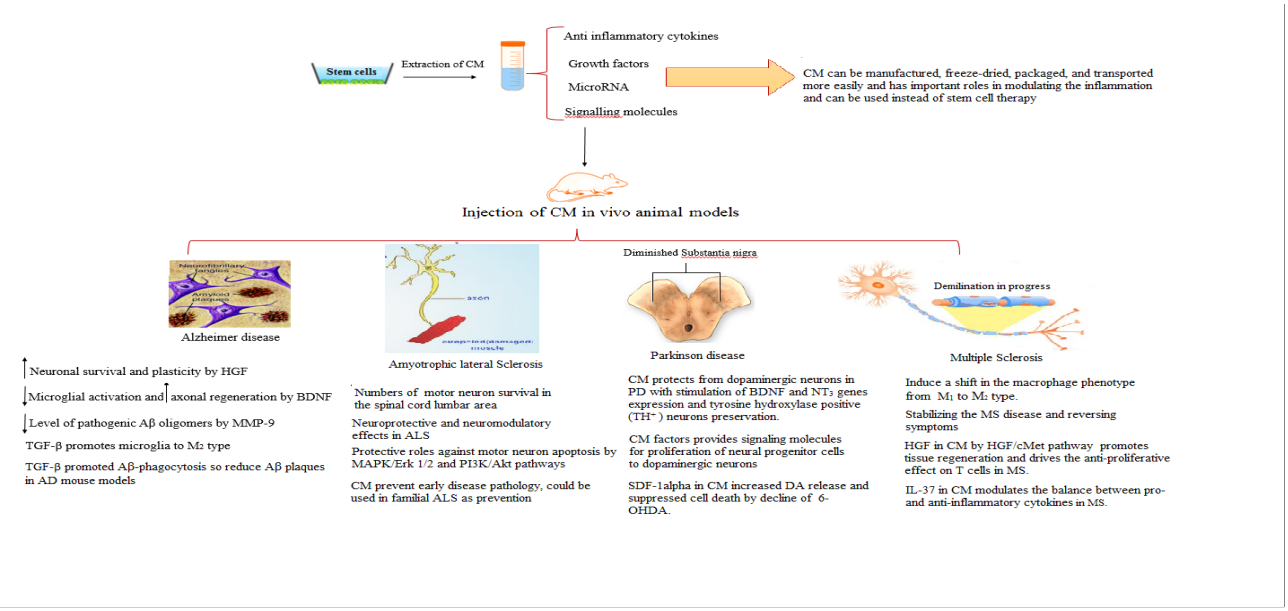
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Tables and Charts:

Figure 1: Summary of CM effects on various neurodegenerative and neuroinflammation disease.



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