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Review Article

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MESENCHYMAL STEM CELLS OBTAINED FROM THE HUMAN UMBILICAL CORD HAVING CAPACITY TO TREATS AILMENTS: A REVIEW

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ABSTACT

The human umbilical cord, a tissue connecting the embryo to the uterus of the mother. Early researchers showcase that the embedded stromal cells were not the only in charge of the Synthesis of matrix components and expansion of the cord, but also for the intercellular communication and constriction. Adult stem cells (ASCs) which can be easily obtained from various tissues, such as the skin, bone marrow, and adipose can be used further to treat disorders of vital bodily organs with less concern than ESCs. Research and different regenerative medicines, which include medicines treating Parkinson's disease, intracerebral hemorrhage, liver disease, brain disease, etc. Different stem cells have been studied to find an effective treatment for this incurable disease. MSCs have an anti-inflammatory effect which reduces the damages in the hepatocytes. The huc-MSCs migrated to the ischemic bounded area, got divided into glial, neuronal, doublecortin, CXCR4+, and the vascular endothelial cells. Also, huc-MSCs thus implanted supported the formation of new vessels to increase the flow of blood, and increase in expression of neuro-tropic factors.

KEYWORDS: Human umbilical cord, intracerebral hemorrhage, brain diseases, MSCs, anti-inflammatory effect, neuro-tropic factors.

INTRODUCTION

The human umbilical cord, a tissue connecting the embryo to the uterus of the mother, comprises of two arteries, one vein, several vessel connective tissue, and an umbilical epithelium. The tissue acting as the connection is often referred to as Wharton's Jelly and is made up of a structure similar to a sponge, weaved by collagen fibers, proteoglycan and stromal cells[1] embedded there. Early researchers showcase that the embedded stromal cells were not the only in charge of the Synthesis of matrix components and expansion of the cord, but also for the intercellular communication and constriction. Similarly, they are also referred to as myofibroblasts.[2,3] However, the studies conducted in 2003 by Mitchel et al[4] suggest that the successful isolation of matrix cells from porcine and the human umbilical cord by explants culture and Romanov et al[5] suggested the isolation of mesenchymal alike cells from a sub-endothelial layer of human umbilical cord vein respectively when extensive researches were done on the umbilical cord-derived MSCs. Two remarkable reviews studying the different characteristics of the cell population with importance given on its niche, isolation, surface markers and primitive properties have been published.[6,7] in these reviews; the main focus is on the recent research on the therapeutic potential of these cells. For convinced, they are referred to as varied types of human umbilical cord-derived cells with characteristics similar to mesenchymal stem.

The past few decades have been a witness for the explosion in the number of stem cell populations that are isolated from the embryonic, fetal and adult tissues. With high self-renewal capacity and the multipotency of differentiating into derivatives of all germ layers in vitro and vivo have made the embryonic stem cell (ESCs) the first choice in tissue engineering research and different regenerative medicines,[8] which include medicines treating Parkinson's disease,[9] amyotrophic lateral sclerosis,[10] spinal cord injury,[11,12] stroke,[13] cardiac arrest,[14] diabetes,[15] hematopoietic diseases,[16] liver diseases,[17] and lung diseases.[18] Along with their ethical and political concerns, their application in health care is limited by their lack of accessibility, technical difficulties in purification and manipulation and also concerns of the formation of teratoma. On the contrary, adult stem cells (ASCs) which can be easily obtained from various tissues, such as the skin, bone marrow, and adipose can be used further to treat disorders of vital bodily organs with less concern than ESCs. However, their application is preferably less keeping in the mind the limited availability, minimal growth, and dividing capacities with an increase in age as well as invasive

harvesting procedures[19] Unlike ESCs, ASC fetal stem cells have a recent history. Over the past few years, two different sources, namely the fetus proper (including fetal bone marrow,[20] lung[21] spleen, liver,[22] pancreas,[23] and peripheral blood [24]) and the supporting extra-embryonic structures (which include umbilical cord blood,[25] umbilical cord,[26] amniotic fluid,[27] placenta,[28] and amnion[29]) can generate putative stem cells. In the past 5 years, MSCs which are obtained from the umbilical cord are of special interest, due to their advantages over its embryonic and adult counterparts. For the uninitiated, umbilical cord is regularly discarded at parturition, therefore the ethical controversy attends the harvest of the resident stem cells population when compared with ethical concerns, plague the isolation of ESCs. Next, the extracorporeal nature of the source facilitates the isolation by the elimination invasion and discomfort in the extraction process and also puts the patient at risk. More significantly, the comparable large volume of the umbilical cord and the ease of physical manipulation theoretically increase the availability of stem cells, which makes it possible to get the required numbers, without any need of long term culture and extensive expansion ex vivo. Above all this based on the duration of generation and sequestration during its early developing stages of ontogenesis, the umbilical cord may bestow the resident stem cell populations with an enhancement in its potential. In the following, we conclude that recent research of huc-MSCs with special emphasis on their plasticity and capable application in the treatment of a large number of diseases.

Effect on Spinal Cord Injury

Stem cell Administration is an appropriate therapeutic strategy for injuries in the spinal cord as demonstrated by research is done in the past on transplantation of ESCs,[30] neutral stem cells, olfactory ensheathing cells, MSCs,[31] umbilical cord blood cells[32] in animals. There are still several significant hurdles to overcome before these researches are put into use, which comprises the identification of the source of stem cells, optimization of their characteristics before transplant, reduction of risks of stem cells, development of large-scale manufacturing technologies.[33] Trustworthy research by Yang et al advocates that transplantation of huc-MSCs obtained from Wharton's Jelly was a useful way to increase the regenerative capacity of corticospinal fibers and locomotor recovery after spinal cord transection in rats. After the transplantation for several weeks, of huc-MSCs in the lesion site of the spine in injured rats, improvement in locomotive activities was recorded with fewer astrocytes in the lesion site with was supported by the regeneration of axons in the corticospinal tract and neurofilament-positive fibers in the lesion site.[34] Also, the transplanted huc-MSCs had a survival of 16 weeks, after a migration from the implantation site for about 1.5 mm in the caudal direction of the rostrocaudal axis, which produces large amounts of human neutrophil-activating protein-2, NT-3, glucocorticoid-induced tumor necrosis factor receptors and VEGF receptor in the spine, which helps the spinal cord in its maintenance. The author thus concludes that the mechanism behind the promotive effect on the regeneration of severed corticospinal axons after the placement of huc-MSCs was probably through the release of more cytokines or factors affecting growth from the undivided cells into the neuronal or glial cells. It also indicates that the implanted huc-MSCs can control the activities of the microglia and reactive astrocytes. 34 The Wharton's Jelly cells derived from neurospheres were implanted along with BDNF into the operated spinal cord of the rats, few of the grafted cells were alive, with an enhancement in the Basso, Beatrice, Bresnahan BBB accreditation, caused an increment in axonal regeneration with the reduction in the number of cavitation were recorded. The results also suggest the scheme of improvement in the outcome is strenuous to be examined by the replacement of cells, with the axonal regeneration and neuroprotective activities induced by grafted cells are probable mechanisms.[35]

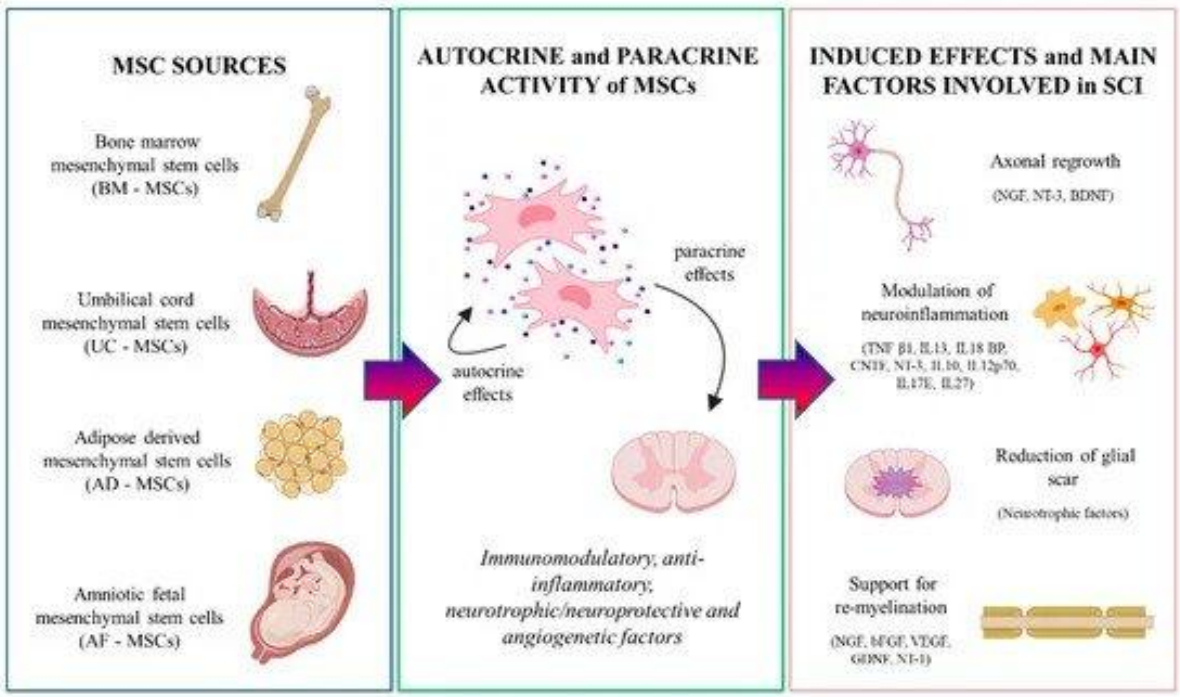

Fig. 1: Mechanisms of MSCs for Spinal cord injury.[44]

Effect on Brain Injury

In curiosity, if BDNF modified huc-MSCs could help stem cells differentiation into neurons and promote neuromotor activities after any injury in the brain, the researchers regulated transfected huc-MSCs at the edge of cerebral lesion of athymic brain injury models of rats, occurring due to hydraulic pressure percussion. The studies show that the newly modified gene huc-MSCs could enhance neurological functions and develop neuron-specific enolase (NSE)- positive cells with lesser (GFAP)-positive cells and apoptosis cells, which signal their possible inclusion in cerebral injury.[36]

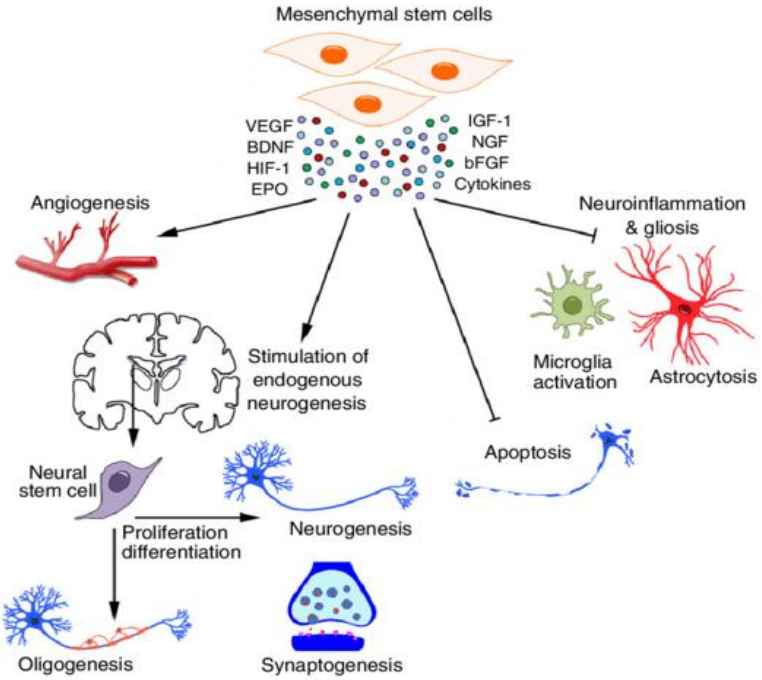

Fig. 2: Mechanisms of MSCs for Brain injury.[43]

Effect on Intracerebral Hemorrhage

In research regarding the therapeutic capacity of huc-MSCs in intracerebral hemorrhage, transplantation of CM-Dil cells into the hemorrhage rat models was done by the help of an injection of bacterial collagenase Vll. The outcome showed improvisation in neurological functions, an increase in vascular density in the lesion and diminished injury volume. Also, comparatively

fewer leukocytes infiltration, microglial activation, reaction at the oxygen species level and matrix metalloproteinase's expression in a peri-CH area in groups were identified when compared with the PBS control group. Thus, it can be concluded that the intracerebral regulation of huc-MSCs accelerates neurological functions in rats. The mechanism behind this may attribute to their ability to terminate inflammation and promote angiogenesis.[37]

Effect on Parkinson's Disease

Parkinson's disease is particularly a neurodegenerative disorder, occurring due to the progressive loss of striatal dopaminergic activity. Up till now, different stem cells have been studied to find an effective treatment for this incurable disease.[40] Fu et al[39] explored that transplantation of huc-MSCs into striatal of the rats suffering from Parkinson's could partly correct the amphetamine evoked rotation caused by the lesion. The cells placed, had a survival of 4 months in vivo and were identified by positive the stain and had migrated for approximately 1.4 mm rostrally and caudally. Following the transplant, about 1000 huc-MSCs were identified in the striatum of hemiparkinsonian rats with no evidence of immune suppression. Weiss et al explored that the apomorphine caused rotations in amelioration in the pilot test with no signs of brain tumor formations or Frank host immune rejection response. Also, the positive DA neurons showed a connection between the number of cells and apomorphine caused by the rotations. As a summary, the recovery of PD model animals probably can contribute to the survival of the degeneration of the DA neurons in the SN and VTA.[38]

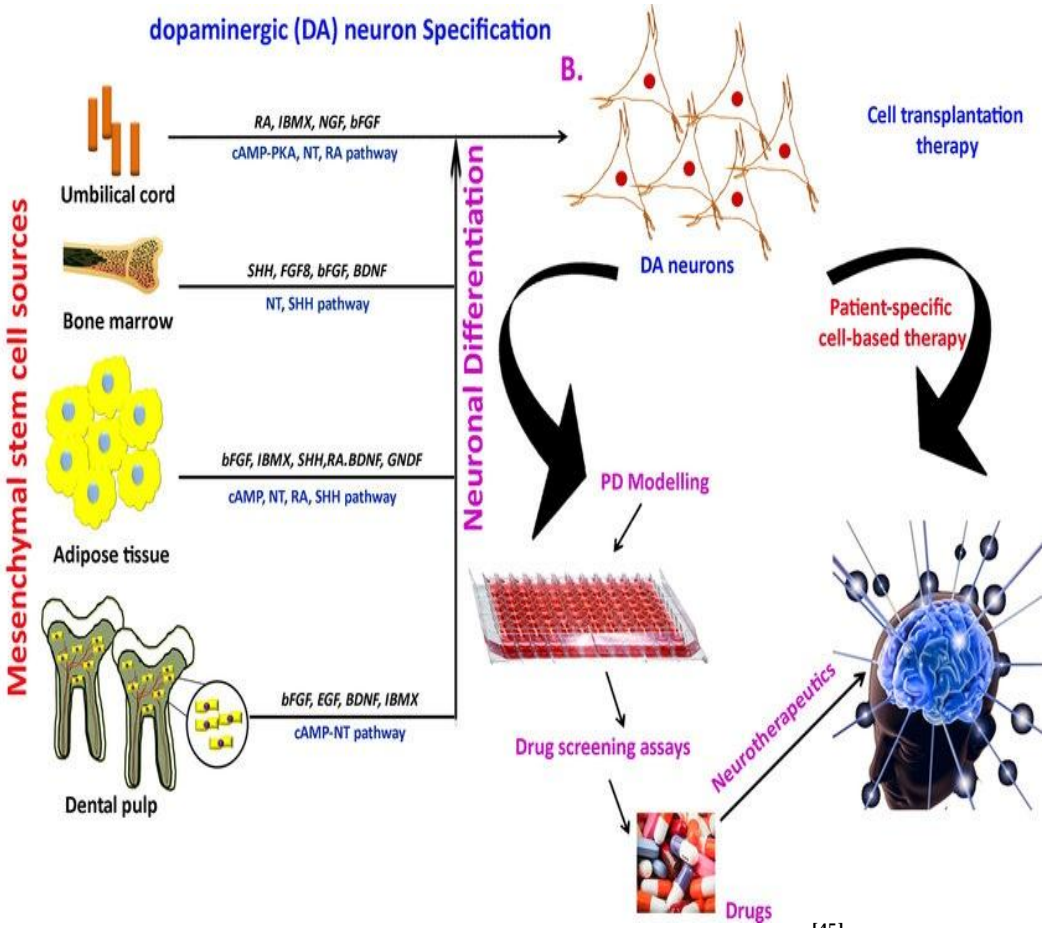

Fig. 3: Mechanisms of MSCs for Parkinson's disease.[45]

Effect on Liver Disease

The mechanisms of MSCs treating liver diseases are studied from different sources. MSCs have an anti-inflammatory effect which reduces the damages in the hepatocytes. These decrease the inflammation in hepatocytes, reduce activities of the hepatic stellate cells and influence the MSCs to reduce activation of hepatic stellate cells. Also, it has been noticed that it affects macrophages too. MSCs change the polarity of the macrophages into an anti-inflammatory counterpart, increasing the production of matrix metalloproteinase to inhibit ECM, increase the capacity of phagocytosis. When monitored, MSCs with macrophages expressed by culturing bone marrow cells for a week, the host macrophages and neutrophils were placed in the liver.[41]

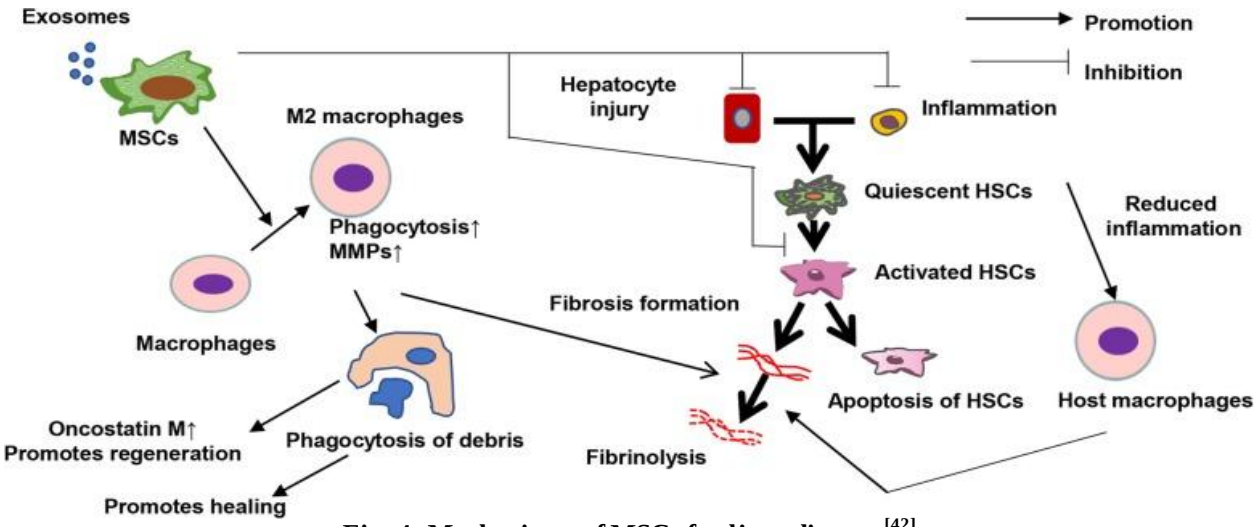

Fig. 4: Mechanisms of MSCs for liver disease.[42]

Effect on Cerebral Ischemic

Ischemic stroke, followed by the neurological injury due to interrupted blood flow to the brain, is a medical condition that may cause permanent neurological damage and even death if not treated in time. As a cure for stroke, several novel neuron restoration methods have been studied. Research supports the plan of stem cell transplantation in the treatment of the neurons, as an effective method.[47] In comparison with ESCs, MSCs have greater accessibility. Ding et al transplanted around 1x106 huc-MSCs into the cortex of middle cerebral artery occlusion in rats and noticed an improvement in the neurological functions and cortical neuronal functions. The huc-MSCs migrated to the ischemic bounded area, got divided into glial, neuronal, doublecortin, CXCR4+, and the vascular endothelial cells.[46] Also, huc-MSCs thus implanted supported the formation of new vessels to increase the flow of blood and an increase in expression of neuro-tropic factors. The researchers suggest that the stem cell-derived macrophages increase B1-integrin and thus improve the angiogenic foundation and plasticity of the brain after transplantation. After this process, 6x105 huc-MSCs obtained from the endothelial layers of the spinal cord into the damaged parts in the rats, improved the neuron function, the nestin-positive endogenous cells in the hippocampus albeit with lesser transplanted cells. They stated that enhancement in the function can be attributed to the neuroprotective effects of huc-MSCs which causes an increase in endogenous neurogenesis and diminishes infarct volume and decrease the formation of new networking between host and the transplanted cells. Also, other reports suggest that implanted huc-MSCs have a survival rate of about 5 weeks in the brain, reducing injury density and functions of the neuron of the rats, an increase in vascular volume in an ipsilateral zone of the stroke. Thus, the mechanism behind the enhancement of the recovery of the neurological functions after the transplantation could have been supported by angiogenesis.[48]

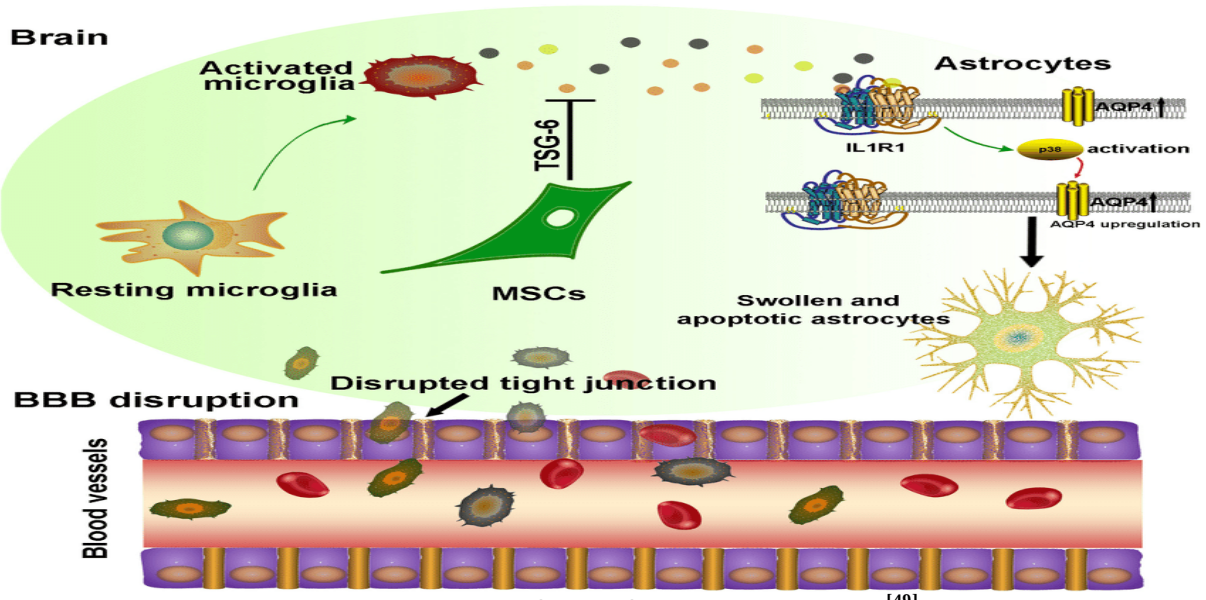

Fig. 5: Mechanisms of MSCs for cerebral ischemic.[49]

Immunosuppressive And Immunomodulatory Effects
MSC arouses negligible immune reactivity that may lead to immunosuppressive and immunomodulatory effects.[50] Research suggests that the immune properties of huc-MSCs inhibit splenocyte proliferation as a response to concanavalin-A stimulus and proliferation of active T cells in a 2 methods mixed lymphocyte reaction (MLR) . However, they did not stunt the nonstimulated splenocyte proliferation or caused stimulation in the T cells in a single way MLR.[50] They also secrete molecules helping immune modulation, such as VEGF, lL-6 but not antigens like CD40, CD80 or CD86. A contemporary study indicates the immunomodulatory characteristics and the immunosuppressive effect of MSCs obtained from an adult human tissue, including the bone marrow, adipose, umbilical cord blood, and Wharton's Jelly showcased no noticeable difference in the levels of secretion from unstimulated MSCs and phytohemagglutinin induced T cells proliferation.[52] Cho et al however found that huc-MSCs could be stimulated to secrete MHCll and increase MHCl with IFN-Y in vitro which were negative for MHC-l and MHC-ll. The most important factor, huc-MSCs induce an immune response when injected into an inflamed region or in the ones stimulated with IFN-Y before injecting an injection of MHC mismatched inactivated huc-MSCs do not impact on the immune system.[53] Stem cell and Rep strategies include ejecting allogeneic cells in the affected region or repeated dosage, to achieve the desired result, which affects the immunogenicity of the cells, which may bear implications for function improvement for treatment for affected tissues.

Modification of Genes
MSCs can be genetically upgraded, which changes them into a reliable source for cells and gene therapy and increases their usage in several fields as therapeutic applications such as enhancement of stem cells, speeding up the hematopoietic reconstitution, cure of intense graft versus host diseases, utility in treatment tumor formations, and expressing anticarcinogenic molecules.[54,55] The capacity of MSC in several gene therapies is more trustworthy than of its other counterparts. The site of activation of tumorigenesis supports development in MSCs engineering as a help to find malignant tissues and express anticancer agents, in the tumor environment. Regulation of huc-MSCs secreting interferon-B[56] with or without 5-fluorouracil.[57] was targeted to develop tumors in the lungs and also reduce the burden. Huc-MSCs which are altered to secrete BDNF also improved neurological functions and enhance NSE-positive cells which inhibit GFAP-positive cells and numerous apoptosis cells after being ejected into the edge of lesion site in athymic rats having a brain injury caused by hydraulic pressure percussion. Also, huc-MSCs help in secreting certain naturally active human factor lX and helps as an effective drug for delivering somatic gene therapy of hemophilia B.[58]

If these cells similar to their counterparts of MSCs or NSCs can target intractable cerebral glioma and help in gene therapy with high efficiency is still been studied.[59]

CONCLUSION
The systemic review suggests that in multicellular organisms, stem cells are characterized as cells that can divide unanimously into various cells, to produce more stem cells. They are available in the fetus and well-developed adults with a slight difference in their properties. Ailments that stem cells are capable of treating include diabetes, Parkinson's disease, heart infarction, and several others. Studies indicate its effective use for the correction of infertility in males and females. With a chance to isolate embryonic stem cells, human cloning is also evaluated. Stem cells are a field of infinite research. It helps in the suppression of pain in injury, helps in the regeneration of important cells. They are also researched for obtaining cure for several immune-related diseases.

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