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(REVIEW ARTICLE)

Therapeutic potential of the MSC secretome

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Abstract

In the last two decades, MSCs have gained substantial attention as a potential source for regenerative therapy. This is due to several reasons such as the ability to isolate using non-invasive techniques, the cell's ability to divide into several lineages including those of non-mesodermal origin and the absence of HLA-DR on the surface of the cell. However, immune rejection is still a possibility in the case of MSC transplant and several studies have reported low survivability of these cells in the transplanted tissue. A remedy to this is the use of the MSC secretome which contains molecules released by the cells for immunomodulation and other regulatory behaviours. Interest in the secretome has been increasing with several studies reporting similar regenerative potential when compared to the cells themselves. This review contains a brief account of the therapeutic effects of the MSC secretome in the case of bone, musclular & neural regeneration.

Keywords: MSCs; Secretome; Exosomes; Extracellular Vesicles; Regenerative Therapy

1. Introduction

Mesenchymal stem cells (MSCs) are adult stem cells that can be found and isolated from various sources in the human body. These cells were discovered by Friedenstein et al in 1970 in the bone marrow of guinea pigs [1]. Some of the other locations where MSCs can be found are muscle, dermis, trabecular bone, adipose tissue, periosteum, pericyte, blood, synovial membrane, placenta, umbilical cord and other tissues [2]. Due to the heterogeneous nature MSCs, International Society for Cellular Therapy (ISCT) has defined certain minimum criteria that a cell type must reach to classify as MSCs: 1) plastic-adherence by the cells, 2) ability to differentiate into osteocytes, chondrocytes & adipocytes & 3) presence of certain cell markers, CD73, CD90 and CD105, and the lack of expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR [3].

MSCs have great potential in regenerative medicine as they can differentiate into several cell types of mesodermal origin as well as transdifferentiate into neural cell types [4], [5]. MSCs also have the capacity to modulate the immune system & migrate to sites of injury. Another major reason that makes mesenchymal stem cells advantageous for regenerative medicine is that the cells can be acquired from patients using non-invasive techniques thus, facilitating autologous transplants. Also, since MSCs do not possess HLA-DR on the cell surface, an allogenic transplant will result in a limited immune reaction thus allowing for a successful transplant [6].

However, this is not to say that MSC therapy has no disadvantages. Immune rejections of MSCs still occurs, as well as ectopic tissue formation and the possibility of tumour formation. To remedy these drawbacks there is increasing interest in the secretome of MSCs [7]. The MSC secretome contains several molecular compounds such as cytokines, chemokines, immunomodulatory molecules & growth factors. Also, extracellular vesicles such as exosomes, microvesicles & apoptotic bodies tend to contain paracrine factors secreted by MSCs. Secretions and exosomes of MSCs

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can be used as cell-free therapeutic products for the treatment of various disorders and injuries [8]. Various studies have established that the secretome of MSCs has a similar therapeutic effect in comparison to transplanted MSCs [9].

2. Bone Regeneration

Bone regeneration after injury is difficult in several cases such as patients of advanced age. Improper or failed healing could significantly lower the quality of life of an individual. The MSC secretome shows promising results in aiding the regenerative process [28]. In 2012, a study established the therapeutic effect of Conditioned Media (CM) on bone regeneration in a rat model. They also observed a greater homing of rat MSCs in the treatment group in comparison to the control group [29]. Similarly, a 2016 study observed that CM containing MSC-derived exosomes showed greater bone regeneration in rat models when compared to CM alone [30].

MSC secretome contains several growth factors, one of which is VEGF. A 2017 study established the importance of VEGF in the CM for the angiogenesis of newly formed bone tissue [31]. Also, the MSC secretome has been found to promote osteoclast differentiation even in the presence of osteoclast differentiation inhibitors by regulating the expression of certain master transcription factors [32]. The culture conditions for the production of CM from MSCs also plays a major role in the composition of the secretome. In 2015, a study found that CM from hypoxic MSC culture contained significantly higher concentrations of angiogenic factors in comparison to normoxic conditions [33]. The safety of CM was used for the first time in 2016 when alveolar bone regeneration was carried out using CM on 8 patients. No complications were observed in any of the individuals [34].

In 2017, a scaffold functionalized with MSC-EVs have been shown to promote better bone regeneration as well as vascularization. This could be a novel technique to aid bone healing [35]. However, it is important to note that the microenvironment has a major impact on the outcome of the treatment. The regenerative properties of exosomes were found to be greatly impaired in the case of the exosomes derived from diabetes mellitus type 1 affected MSCs [36].

3. Muscular Regeneration

A 2014 study found that treating a myectomy model with CM from MSCs resulted in less evident scar tissue and better performance in histological scoring [10]. This could be a result of expression of VEGF-α, IGF-1, EGF, keratinocyte growth factor, angiopoietin-1, stromal-derived factor-1, macrophage inflammatory protein-1α and -β and erythropoietin [11]. Mesenchymal stem cell therapy has also been proven to mediate inflammation thus resulting in reduced scar formation [12]. CM has also been known to enhance the proliferation and migration of cells as well as modulate myoblast apoptosis [13].

A study in 2016 discovered that treating atrophied muscles with CM significantly helped in their recovery. This was a result of the activation of the PI3K/AKT pathway which caused the suppression of the atrophy-related ubiquitin E3-ligases, muscle ring finger 1 and muscle atrophy F-box and the elevated expression of desmin and skeletal muscle actin [14], [15]. CM can also help heal muscle injury caused as a result of vaginal birth [16]. Similarly, CM has been proven to heal eccentric contraction muscle injury by increasing the expression of the PI3K/AKT pathway in a 2021 study [17]. Extracellular Vesicles (EVs) of MSCs have also been established for their therapeutic potential to regenerate skeletal muscle in case of acute injury. This mechanism seems to work differently but synergistically with the soluble secretome of MSCs [18].

4. Neural Regeneration

Neurodegenerative diseases are a major class of diseases that affect the life expectancy and the quality of life of a significant portion of the population. The therapeutic effect of MSC secretome & exosomes for neurodegenerative diseases has been established across multiple studies [19], [20]. A study carried out in 2015 proved that the secretome of MSCs resulted in neuronal differentiation both in vitro & in vivo [21]. Exogenous CX3CL1 released from MSCs can switch microglia from a detrimental phenotype to a neuroprotective phenotype which can be useful in the treatment of Alzheimer's Disease [22]. Endogenous IL-6 derived from MSCs can cause a significant reduction in autophagy in damaged hippocampal neurons. It does so by inhibiting the AMPK/mTOR pathway [23]. Also, MSC-derived IL-6 activated the AMPK/mTOR pathway in astrocytes to inhibit their proliferation in the case of hypoxic- ischemic brain damage [24].

Injecting the MSC secretome directly into a Parkinson's Disease rat model has yielded positive results albeit with decreasing effect with passing time. The treatment resulted in an increase in dopaminergic neurons & neuronal

terminals thus facilitating improvement in motor functions. Upon analysing the secretome, several neuroregulatory compounds such as cystatin C, glia-derived nexin, galectin-1, pigment epithelium-derived factor, vascular endothelial growth factor, brain-derived neurotrophic factor, interleukin-6, and glial cell line-derived neurotrophic factor were identified in the milieu [25]. The MSC secretome in combination with brain-derived neurotrophic factor (BDNF) has been proven to give significantly better neuroprotection in case of intracerebral haemorrhage than BDNF alone [26]. Also, the secretome can be used for oligodendrogenesis from adult neural stem cells as a result of multiple differentiation proteins present in the secretome including TIMP-1 [27].

5. Conclusion

MSC secretome & extracellular vesicles have been proven, using various studies, to have tremendous therapeutic potential in the case of various diseases and injuries spanning several different biological systems. With clinical trials underway, apart from establishing its efficacy and route of administration, it is imperative to conduct various safety assessments, to ensure no ill-effects occur as a result of its use. With the momentum of the current research, MSC secretome- or extracellular vesicle-based therapy might be a reality in the near future.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] A. J. Friedenstein, R. K. Chailakhjan, and K. S. Lalykina, The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells, Cell Tissue Kinet., vol. 3, no. 4, pp. 393–403, Oct. 1970, doi: 10.1111/j.1365-2184.1970.tb00347.x.

[2] R. Mafi, S. Hindocha, P. Mafi, M. Griffin, and W. S. Khan, Sources of Adult Mesenchymal Stem Cells Applicable for Musculoskeletal Applications - A Systematic Review of the Literature, Open Orthop. J., vol. 5, pp. 242–248, Jul. 2011, doi: 10.2174/1874325001105010242.

[3] M. Dominici et al., Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement, Cytotherapy, vol. 8, no. 4, pp. 315–317, Jan. 2006, doi: 10.1080/14653240600855905.

[4] R. Hernández, C. Jiménez-Luna, J. Perales-Adán, G. Perazzoli, C. Melguizo, and J. Prados, Differentiation of Human Mesenchymal Stem Cells towards Neuronal Lineage: Clinical Trials in Nervous System Disorders, Biomol. Ther., vol. 28, no. 1, pp. 34–44, Jan. 2020, doi: 10.4062/biomolther.2019.065.

[5] N. S. Hwang, C. Zhang, Y.-S. Hwang, and S. Varghese, Mesenchymal stem cell differentiation and roles in regenerative medicine, Wiley Interdiscip. Rev. Syst. Biol. Med., vol. 1, no. 1, pp. 97–106, 2009, doi: 10.1002/wsbm.26.

[6] H. Kupcova Skalnikova, Proteomic techniques for characterisation of mesenchymal stem cell secretome, Biochimie, vol. 95, no. 12, pp. 2196–2211, Dec. 2013, doi: 10.1016/j.biochi.2013.07.015.

[7] G. Műzes and F. Sipos, Mesenchymal Stem Cell-Derived Secretome: A Potential Therapeutic Option for Autoimmune and Immune-Mediated Inflammatory Diseases, Cells, vol. 11, no. 15, p. 2300, Jul. 2022, doi: 10.3390/cells11152300.

[8] J. R. Ferreira, G. Q. Teixeira, S. G. Santos, M. A. Barbosa, G. Almeida-Porada, and R. M. Gonçalves, Mesenchymal Stromal Cell Secretome: Influencing Therapeutic Potential by Cellular Pre-conditioning, Front. Immunol., vol. 9, 2018, Accessed: Aug. 26, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fimmu.2018.02837

[9] M. Gnecchi et al., Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol., vol. 20, no. 6, pp. 661–669, Apr. 2006, doi: 10.1096/fj.05-5211com.

[10] T. Pereira et al., Effects of Human Mesenchymal Stem Cells Isolated from Whartons Jelly of the Umbilical Cord and Conditioned Media on Skeletal Muscle Regeneration Using a Myectomy Model, Stem Cells Int., vol. 2014, p. 376918, 2014, doi: 10.1155/2014/376918.

[11] L. Chen, E. E. Tredget, P. Y. G. Wu, and Y. Wu, Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing, PloS One, vol. 3, no. 4, p. e1886, Apr. 2008, doi: 10.1371/journal.pone.0001886.

[12] W. M. Jackson, L. J. Nesti, and R. S. Tuan, Mesenchymal stem cell therapy for attenuation of scar formation during wound healing, Stem Cell Res. Ther., vol. 3, no. 3, p. 20, May 2012, doi: 10.1186/scrt111.

[13] M. Aslam et al., Bone marrow stromal cells attenuate lung injury in a murine model of neonatal chronic lung disease, Am. J. Respir. Crit. Care Med., vol. 180, no. 11, pp. 1122–1130, Dec. 2009, doi: 10.1164/rccm.200902-0242OC.

[14] M. J. Kim, Z.-H. Kim, S.-M. Kim, and Y.-S. Choi, Conditioned medium derived from umbilical cord mesenchymal stem cells regenerates atrophied muscles, Tissue Cell, vol. 48, no. 5, pp. 533–543, Oct. 2016, doi: 10.1016/j.tice.2016.06.010.

[15] M. Sandonà et al., Mesenchymal Stromal Cells and Their Secretome: New Therapeutic Perspectives for Skeletal Muscle Regeneration, Front. Bioeng. Biotechnol., vol. 9, 2021, Accessed: Aug. 26, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fbioe.2021.652970

[16] K. Deng et al., Mesenchymal stem cells and their secretome partially restore nerve and urethral function in a dual muscle and nerve injury stress urinary incontinence model, Am. J. Physiol.-Ren. Physiol., vol. 308, no. 2, pp. F92–F100, Jan. 2015, doi: 10.1152/ajprenal.00510.2014.

[17] R. Squecco et al., Bone Marrow-Mesenchymal Stromal Cell Secretome as Conditioned Medium Relieves Experimental Skeletal Muscle Damage Induced by Ex Vivo Eccentric Contraction, Int. J. Mol. Sci., vol. 22, no. 7, Art. no. 7, Jan. 2021, doi: 10.3390/ijms22073645.

[18] R. Mitchell et al., Secretome of adipose-derived mesenchymal stem cells promotes skeletal muscle regeneration through synergistic action of extracellular vesicle cargo and soluble proteins, Stem Cell Res. Ther., vol. 10, no. 1, p. 116, Apr. 2019, doi: 10.1186/s13287-019-1213-1.

[19] A. Luarte, L. F. Bátiz, U. Wyneken, and C. Lafourcade, Potential Therapies by Stem Cell-Derived Exosomes in CNS Diseases: Focusing on the Neurogenic Niche, Stem Cells Int., vol. 2016, p. e5736059, Apr. 2016, doi: 10.1155/2016/5736059.

[20] M. Ghasemi, E. Roshandel, M. Mohammadian, B. Farhadihosseinabadi, P. Akbarzadehlaleh, and K. Shamsasenjan, Mesenchymal stromal cell-derived secretome- based therapy for neurodegenerative diseases: overview of clinical trials, Stem Cell Res. Ther., vol. 14, no. 1, p. 122, May 2023, doi: 10.1186/s13287-023-03264-0.

[21] F. G. Teixeira et al., Secretome of mesenchymal progenitors from the umbilical cord acts as modulator of neural/glial proliferation and differentiation, Stem Cell Rev. Rep., vol. 11, no. 2, pp. 288–297, Apr. 2015, doi: 10.1007/s12015-014-9576-2.

[22] D. Giunti et al., Mesenchymal stem cells shape microglia effector functions through the release of CX3CL1, Stem Cells Dayt. Ohio, vol. 30, no. 9, pp. 2044–2053, Sep. 2012, doi: 10.1002/stem.1174.

[23] M. Yang et al., Mesenchymal Stromal Cells Suppress Hippocampal Neuron Autophagy Stress Induced by Hypoxic-Ischemic Brain Damage: The Possible Role of Endogenous IL-6 Secretion, Neural Plast., vol. 2020, p. 8822579, 2020, doi: 10.1155/2020/8822579.

[24] M. He, X. Shi, M. Yang, T. Yang, T. Li, and J. Chen, Mesenchymal stem cells-derived IL-6 activates AMPK/mTOR signaling to inhibit the proliferation of reactive astrocytes induced by hypoxic-ischemic brain damage, Exp. Neurol., vol. 311, pp. 15–32, Jan. 2019, doi: 10.1016/j.expneurol.2018.09.006.

[25] F. G. Teixeira et al., Impact of the Secretome of Human Mesenchymal Stem Cells on Brain Structure and Animal Behavior in a Rat Model of Parkinsons Disease, Stem Cells Transl. Med., vol. 6, no. 2, pp. 634–646, Feb. 2017, doi: 10.5966/sctm.2016-0071.

[26] M. Karagyaur et al., MSC Secretome as a Promising Tool for Neuroprotection and Neuroregeneration in a Model of Intracerebral Hemorrhage, Pharmaceutics, vol. 13, no. 12, p. 2031, Nov. 2021, doi: 10.3390/pharmaceutics13122031.

[27] I. Samper Agrelo et al., Secretome Analysis of Mesenchymal Stem Cell Factors Fostering Oligodendroglial Differentiation of Neural Stem Cells In Vivo, Int. J. Mol. Sci., vol. 21, no. 12, p. 4350, Jun. 2020, doi: 10.3390/ijms21124350.

[28] D. Marolt Presen, A. Traweger, M. Gimona, and H. Redl, Mesenchymal Stromal Cell-Based Bone Regeneration Therapies: From Cell Transplantation and Tissue Engineering to Therapeutic Secretomes and Extracellular Vesicles, Front. Bioeng. Biotechnol., vol. 7, 2019, Accessed: Aug. 27, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fbioe.2019.00352

[29] M. Osugi, W. Katagiri, R. Yoshimi, T. Inukai, H. Hibi, and M. Ueda, Conditioned Media from Mesenchymal Stem Cells Enhanced Bone Regeneration in Rat Calvarial Bone Defects, Tissue Eng. Part A, vol. 18, no. 13–14, pp. 1479–1489, Jul. 2012, doi: 10.1089/ten.tea.2011.0325.

[30] T. Furuta et al., Mesenchymal Stem Cell-Derived Exosomes Promote Fracture Healing in a Mouse Model, Stem Cells Transl. Med., vol. 5, no. 12, pp. 1620–1630, Dec. 2016, doi: 10.5966/sctm.2015-0285.

[31] W. Katagiri et al., Angiogenesis in newly regenerated bone by secretomes of human mesenchymal stem cells, Maxillofac. Plast. Reconstr. Surg., vol. 39, no. 1, p. 8, Mar. 2017, doi: 10.1186/s40902-017-0106-4.

[32] K. Ogata, W. Katagiri, and H. Hibi, Secretomes from mesenchymal stem cells participate in the regulation of osteoclastogenesis in vitro, Clin. Oral Investig., vol. 21, no. 6, pp. 1979–1988, Jul. 2017, doi: 10.1007/s00784-016-1986-x.

[33] M. Fujio et al., Conditioned media from hypoxic-cultured human dental pulp cells promotes bone healing during distraction osteogenesis, J. Tissue Eng. Regen. Med., vol. 11, no. 7, pp. 2116–2126, 2017, doi: 10.1002/term.2109.

[34] W. Katagiri, M. Osugi, T. Kawai, and H. Hibi, First-in-human study and clinical case reports of the alveolar bone regeneration with the secretome from human mesenchymal stem cells, Head Face Med., vol. 12, no. 1, p. 5, Jan. 2016, doi: 10.1186/s13005-016- 0101-5.

[35] H. Xie et al., Extracellular Vesicle-functionalized Decalcified Bone Matrix Scaffolds with Enhanced Pro-angiogenic and Pro-bone Regeneration Activities, Sci. Rep., vol. 7, no. 1, Art. no. 1, Apr. 2017, doi: 10.1038/srep45622.

[36] Y. Zhu, Y. Jia, Y. Wang, J. Xu, and Y. Chai, Impaired Bone Regenerative Effect of Exosomes Derived from Bone Marrow Mesenchymal Stem Cells in Type 1 Diabetes, Stem Cells Transl. Med., vol. 8, no. 6, pp. 593–605, Jun. 2019, doi: 10.1002/sctm.18-0199.