Review Article

Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_17_18

Encapsulated stem cells ameliorate depressive-like behavior via growth factor secretion

Kyohei Kin, Takao Yasuhara, Cesar V Borlongan[1], Isao Date

Abstract:

As prevalence of depression continues to rise around the world, there remains a stagnation of available treatments as the affected population grows. The subset of treatment-resistant depression also is on the rise highlighting the need for innovative treatments to address this issue. Mesenchymal stem cells (MSCs) have been reported to attenuate depression-like behaviors, however, the effects of encapsulation of MSCs have yet to be investigated. Encapsulation of MSCs exhibited prolonged survival of exogenous cell injection accompanied with increased secretion of neurotrophic factors including vascular endothelial growth factor, ciliary neurotrophic factor, and others. The enhanced expression of these factors highlights the ability of encapsulated MSCs to upregulate the respective signaling pathways, which are associated with depression pathology and activation of neurogenesis. This treatment identifies a promising therapeutic option for depression, specifically treatment-resistant depression. Further, evaluation of long-term effects of the treatment is warranted. This paper is a review article. Referred literature in this paper has been listed in the references section. The datasets supporting the conclusions of this article are available online by searching various databases including PubMed. Some original themes in this article come from the laboratory practice in our research center and the authors' experiences.

Keywords:

Animal model, depression, growth factors, mesenchymal, transplantation

Introduction

Depression is a disease that affects one in six individuals in America and may others worldwide.[1,2] Even with continuous progress in pharmacological treatments, only approximately one-half of the patients with clinical depression benefit from current therapies.[3] Thus, there is a pressing therapeutic need for research of treatments that target treatment-resistant depression.[4] Treatment-resistant depression consists of associated risk factors including congenital susceptibility to depression and resistance of common pharmacological therapies.[5] Several preclinical studies, Wistar Kyoto (WKY) rats, show elevated levels of congenital depression-like behavior and exhibit resistance to common treatments, demonstrating their usefulness as a potential model for treatment-resistant depression.[4,6-8]

Mesenchymal stem cells (MSCs) exhibit potential as a therapy for neurodegenerative disease, including, stroke, Parkinson's disease, and multiple sclerosis.[9-11] Several transplantation methods have been investigated to evaluate its effect on depression. Intrahippocampal transplantation of MSCs enhanced neuroplasticity but failed to yield any antidepressant effects within a Lewis rat model.[12] Yet, when transplanted intraventricularly, MSCs produced

Department of Neurological Surgery, Okayama University Graduate School of Medicine, Okayama, Japan, [1]Department of Neurosurgery and Brain Repair, Center of Excellence for Aging and Brain Repair, University of South Florida, Tampa, FL, US

Address for correspondence:
Dr. Takao Yasuhara, Department of Neurological Surgery, Okayama University Graduate School of Medicine, Okayama, Japan.
E-mail: tyasu37@cc.okayama-u.ac.jp

Submission: 25-07-2018
Revised: 04-09-2018
Accepted: 10-09-2018

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kin K, Yasuhara T, Borlongan CV, Date I. Encapsulated stem cells ameliorate depressive-like behavior via growth factor secretion. Brain Circ 2018;4:128-32.

© 2018 Brain Circulation | Published by Wolters Kluwer Health – Medknow

antidepressant effects in Flinders sensitive line rats.[13,14] However, the mechanism of action is currently unknown, specifically if the beneficial effects stem from contact between MSCs and host cells or MSC-secreted factors that alleviate depressive symptoms.

Several studies highlighted the encapsulation of a variety of cell lines, in which neurotrophic factors were suggested to be the therapeutic action in stem cells in numerous diseases.[15-17] Secretion of MSC neurotrophic factors may provide the improved functional outcomes rather than direct survival and integration into the host by the MSC graft.[18] The efficacy of encapsulated MSCs (eMSCs) as a treatment for depression has been relatively unknown up to this point. In this review, we will elucidate the possible mechanism of action and cognitive effects of eMSC in treatment-resistant depression.

Cell Encapsulated Stem Cells and Depression

Although pharmacological advances continue each day, only one-half of the patients who are clinically depressed benefit from current therapies. This highlights the necessity for further research and development of novel treatments, particularly targeting treatment-resistant depression. Despite the reported antidepressant properties of MSCs, the possible benefit of this treatment on treatment-resistant depression has yet to be studied. Cell encapsulation aims to increase survival of transplanted cells, yet the mechanisms and benefits of encapsulated MSCs are unknown. In this review, we discuss the enhanced therapeutic effects of encapsulating MSCs (eMSCs). The transplantation of eMSCs in the lateral ventricle amplified neurogenesis in the dentate gyrus (DG) and subventricular zone of the hippocampus as well as protecting against depressive-like behavior, compared to MSCs without encapsulation and when MSCs were transplanted into the striatum. eMSCs were able to release several neurotrophic factors over a prolonged period including brain-derived neurotrophic factor, ciliary neurotrophic factor (CNTF), fibroblast growth factor-2 and vascular endothelial growth factor (VEGF). Specifically, the transplantation of eMSCs into the lateral ventricle stimulated theses pathways yielding the various neurotrophic factors. The use of eMSC transplantation as a therapy for depression, particularly treatment-resistant depression, is promising but further investigations should be considered to address the long-term effects associated with this treatment.

Discussion

This study showed that eMSCs had improved benefits over the transplantation of nonencapsulated MSCs for *in vivo* treatment-resistant depression models.[19] In prior study, MSCs transplanted in the lateral ventricle (MSC-LV) resulted in antidepressant effects and enhanced neurogenesis in animal models for depression.[13] However, when administered in the present study, MSCs-LV failed to alter behavior or improve neurogenesis in the treatment-resistant depression animal model, although more cells were transplanted than the previously discussed study.[13,19] In contrast, transplantation of eMSCs into the lateral ventricle (eMSC-LV), produced a behavioral as well as increased neurogenesis in rats with treatment-resistant depression.[19] These results support that eMSCs may be an improved therapy when addressing this treatment-resistant depression modality, which is one of the strictest and likely represents a more advanced pathology then typically observed in a clinical setting. Yet, the eMSC-LV antidepressant profile is not common to conventional pharmacological treatments. Typical antidepressant drugs will enhance neurogenesis within the DG only, creating an antidepressant profile of enhanced Forced Swim Test without affecting open-field test, creating difficulty in behavioral assessments.[20] The murky pathology of WKY rats accentuates the complexities of this problem. Future studies using other animal models for depression or battery of behavioral tests could provide further information.

Transplanted MSCs in neurogenerative disease rodent models often exhibit low graft survival and the present study was no different, as no MSCs were found in the lateral ventricle or adjacent brain tissue at 7 days post transplantation.[21-23] Therefore, the overall engraftment rate of transplanted MSCs in the lateral ventricle is very mild in the best case. However, polymer encapsulation could shield the implanted cells from an endogenous immune system reaction.[24] In the present study, eMSCs were demonstrated to survive until at least day 15 following injection, along with secretion of neurotrophic factors (brain-derived neurotrophic factor, CNTF, fibroblast growth factor 2 [FGF-2] and VEGF) from the transplanted eMSC.[19] The encapsulation likely creates an indirect effect by increasing the survival of the MSCs graft, therefore mediating increased levels of neurotrophic factor secretion. As a result, encapsulation encouraged the improved antidepressant effects of transplanted MSCs and enhanced neurogenesis. However, due to the typical treatment length needed to address depression in the clinic the long-term effects of eMSCs are needed to elucidate the effects of long-term cell survival as well as multiple treatments.

The current study targets the lateral ventricle as the most effective site for transplantation over the striatum. As various secreted cytokines of MSCs are suggested

to play a vital role in the beneficial effects of MSCs, the secretome of eMSCs-LV has a greater opportunity to reach distant sites than the secretions of eMSCs ingrafted in the striatum cannot.[18,25] The many complexities of depression pathology remain unknown, and potential culprit lesions distant from the lateral ventricle can cause atypical pathology.[25] The mechanism of delivery of the MSC secretome is an important aspect of the therapeutic potential stem cell transplantation in depression pathologies.

Targeting the efficiency of the secretome instead of MSCs graft survival could be the vital step to enhancing its antidepressant effects. When MSCs are transplanted into the lateral ventricle, they travel to the ipsilateral hippocampus, yet when the hippocampus is targeted for direct injection of MSCs, there are no significant antidepressant effects in rodent depression models.[12,13,26] Evidence is shown that the administration of eMSCs-LV ameliorates depressive-like behavior, signifying that migration nor transplantation of MSCs into the hippocampus are necessary for the beneficial antidepressant effects to be present.

To further substantiate the roles of trophic factors in the eMSCs-mediated antidepressant effects, phosphorylation of FGRFR1, TrkB, and VEGFR2, which are receptors for FGF-2, BDNF, and VEGF, respectively were measured. eMSCs were responsible for secreting enhanced levels of BDNF, FGF-2, and VEGF and upregulating the phosphorylation related receptors for each factor.[19] This suggests that eMSCs-LV stimulate the pathways of FGF-2, BDNF, and VEGF which notably are pathways related to pathological depression as well as regulating neurogenesis.[19,25,27-35] The injection of any of the aforementioned factors into the lateral ventricle or the DG yield antidepressant effects.[33,36,37]

Additional investigation focused on the relationship between depression and neurogenesis, utilizing CNTF, which is shown to affect depressive-like behavior, anxiety, and promote neurogenesis.[38-40] To monitor the CNTF pathway, expression of STAT3 and phosphorylated STAT3 (pSTAT3) were monitored. STAT3 is a product of the CNTF pathway, and pSTAT3 is created by CNTF pathway activation.[41,42] In the present study, eMSCs were found to release CNTF and upregulation pSTAT3 expression, indicating the CNTF pathway was stimulated by transplantation of eMSCs-LV. In a previous study, a capsule-releasing CNTF, injected into the lateral ventricle, rescued motor function in aged rats.[42] The exhibited changes in behavioral deficits following eMSCs-LV treatment could involve the CNTF pathway and therefore implicate the Jak-STAT pathway as a positive autoregulatory loop.[33,43,44] These pathways are likely only a portion of the many potential signaling pathways that regulated the neurogenic activity in depression pathology.

In lockstep with the examination of the function of neurogenesis in depression, eMSCs-LV were demonstrated to elevate the expression of CNTF, CNTFR-alpha (receptor of CNTF), VEGF, and VEGFR2.[19] The enhanced expression of VEGF is similar to stroke animal models.[45,46] When dental pulp cells, which have a similar phenotype as MSCs, are injected into the hippocampus they also increase the levels of VEGF and CNTF by the brain, suggesting the benefits of a conducive microenvironment within the brain to yield an antidepressant effect.[47] The role of CNTF in an autocrine manner compared to VEGFR2, which is vital for neurogenesis, highlights the intimate relationship between neurogenesis and depressive-like behavior in creating an antidepressant effect.[38,39,48-50]

Further studies need to address the inability to identify either neurogenesis, neurotrophic factors or potentially both as the chief component of the therapeutic effects of eMSCs-LV. Furthermore, evaluating the efficacy of the previously mentioned neurotrophic factors by directly injecting them into the lateral ventricle may elucidate their role and lead to a novel therapeutic modality for the depression model. In essence, eMSCs-LV fostered an antidepressant effect in the rodent treatment-resistant depression model. Encapsulation of MSCs prolongs the secretion of exogenous neurotrophic factors while eliciting the release of endogenous neurotrophic factors and promoting neurogenesis, altogether highlights the therapeutic potential of stem cell therapy as a treatment for depression.[51,52]

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature 2008;455:894-902.
2. Thornicroft G, Chatterji S, Evans-Lacko S, Gruber M, Sampson N, Aguilar-Gaxiola S, *et al.* Undertreatment of people with major depressive disorder in 21 countries. Br J Psychiatry 2017;210:119-24.
3. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al.* Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am J Psychiatry 2006;163:1905-17.
4. Willner P, Belzung C. Treatment-resistant depression: Are animal models of depression fit for purpose? Psychopharmacology (Berl) 2015;232:3473-95.
5. Willner P, Scheel-Krüger J, Belzung C. Resistance to antidepressant drugs: The case for a more predisposition-based

and less hippocampocentric research paradigm. Behav Pharmacol 2014;25:352-71.
6. López-Rubalcava C, Lucki I. Strain differences in the behavioral effects of antidepressant drugs in the rat forced swimming test. Neuropsychopharmacology 2000;22:191-9.
7. Will CC, Aird F, Redei EE. Selectively bred wistar-kyoto rats: An animal model of depression and hyper-responsiveness to antidepressants. Mol Psychiatry 2003;8:925-32.
8. Tejani-Butt S, Kluczynski J, Paré WP. Strain-dependent modification of behavior following antidepressant treatment. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:7-14.
9. Glavaski-Joksimovic A, Bohn MC. Mesenchymal stem cells and neuroregeneration in Parkinson's disease. Exp Neurol 2013;247:25-38.
10. Zhang ZG, Chopp M. Neurorestorative therapies for stroke: Underlying mechanisms and translation to the clinic. Lancet Neurol 2009;8:491-500.
11. Karussis D, Kassis I, Kurkalli BG, Slavin S. Immunomodulation and neuroprotection with mesenchymal bone marrow stem cells (MSCs): A proposed treatment for multiple sclerosis and other neuroimmunological/neurodegenerative diseases. J Neurol Sci 2008;265:131-5.
12. Coquery N, Blesch A, Stroh A, Fernández-Klett F, Klein J, Winter C, *et al.* Intrahippocampal transplantation of mesenchymal stromal cells promotes neuroplasticity. Cytotherapy 2012;14:1041-53.
13. Tfilin M, Sudai E, Merenlender A, Gispan I, Yadid G, Turgeman G, *et al.* Mesenchymal stem cells increase hippocampal neurogenesis and counteract depressive-like behavior. Mol Psychiatry 2010;15:1164-75.
14. Overstreet DH, Wegener G. The flinders sensitive line rat model of depression–25 years and still producing. Pharmacol Rev 2013;65:143-55.
15. Yasuhara T, Shingo T, Kobayashi K, Takeuchi A, Yano A, Muraoka K, *et al.* Neuroprotective effects of vascular endothelial growth factor (VEGF) upon dopaminergic neurons in a rat model of Parkinson's disease. Eur J Neurosci 2004;19:1494-504.
16. Yano A, Shingo T, Takeuchi A, Yasuhara T, Kobayashi K, Takahashi K, *et al.* Encapsulated vascular endothelial growth factor-secreting cell grafts have neuroprotective and angiogenic effects on focal cerebral ischemia. J Neurosurg 2005;103:104-14.
17. Kuramoto S, Yasuhara T, Agari T, Kondo A, Jing M, Kikuchi Y, *et al.* BDNF-secreting capsule exerts neuroprotective effects on epilepsy model of rats. Brain Res 2011;1368:281-9.
18. Paul G, Anisimov SV. The secretome of mesenchymal stem cells: Potential implications for neuroregeneration. Biochimie 2013;95:2246-56.
19. Kin K, Yasuhara T, Kameda M, Tomita Y, Umakoshi M, Kuwahara K, *et al.* Cell encapsulation enhances antidepressant effect of the mesenchymal stem cells and counteracts depressive-like behavior of treatment-resistant depressed rats. Mol Psychiatry. 2018. doi: 10.1038/s41380-018-0208-0. [Epub ahead of print].
20. Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000;20:9104-10.
21. Liu N, Chen R, Du H, Wang J, Zhang Y, Wen J, *et al.* Expression of IL-10 and TNF-alpha in rats with cerebral infarction after transplantation with mesenchymal stem cells. Cell Mol Immunol 2009;6:207-13.
22. Long Q, Li J, Luo Q, Hei Y, Wang K, Tian Y, *et al.* MRI tracking of bone marrow mesenchymal stem cells labeled with ultra-small superparamagnetic iron oxide nanoparticles in a rat model of temporal lobe epilepsy. Neurosci Lett 2015;606:30-5.
23. Ruzicka J, Kulijewicz-Nawrot M, Rodrigez-Arellano JJ, Jendelova P, Sykova E. Mesenchymal stem cells preserve working memory in the 3xTg-AD mouse model of Alzheimer's disease. Int J Mol Sci 2016;17. pii: E152.
24. Date I, Ohmoto T, Imaoka T, Ono T, Hammang JP, Francis J, *et al.* Cografting with polymer-encapsulated human nerve growth factor-secreting cells and chromaffin cell survival and behavioral recovery in hemiparkinsonian rats. J Neurosurg 1996;84:1006-12.
25. Krishnan V, Nestler EJ. Linking molecules to mood: New insight into the biology of depression. Am J Psychiatry 2010;167:1305-20.
26. Shwartz A, Betzer O, Kronfeld N, Kazimirsky G, Cazacu S, Finniss S, *et al.* Therapeutic effect of astroglia-like mesenchymal stem cells expressing glutamate transporter in a genetic rat model of depression. Theranostics 2017;7:2690-703.
27. Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S, *et al.* Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci 2005;255:381-6.
28. Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G, *et al.* Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 2005;57:1068-72.
29. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: A meta-analysis. Am J Psychiatry 2004;161:598-607.
30. Gómez-Pinilla F, Dao L, Choi J, Ryba EA. Diazepam induces FGF-2 mRNA in the hippocampus and striatum. Brain Res Bull 2000;53:283-9.
31. Maragnoli ME, Fumagalli F, Gennarelli M, Racagni G, Riva MA. Fluoxetine and olanzapine have synergistic effects in the modulation of fibroblast growth factor 2 expression within the rat brain. Biol Psychiatry 2004;55:1095-102.
32. Mallei A, Shi B, Mocchetti I. Antidepressant treatments induce the expression of basic fibroblast growth factor in cortical and hippocampal neurons. Mol Pharmacol 2002;61:1017-24.
33. Warner-Schmidt JL, Duman RS. VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants. Proc Natl Acad Sci U S A 2007;104:4647-52.
34. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925-35.
35. Turner CA, Clinton SM, Thompson RC, Watson SJ Jr., Akil H. Fibroblast growth factor-2 (FGF2) augmentation early in life alters hippocampal development and rescues the anxiety phenotype in vulnerable animals. Proc Natl Acad Sci U S A 2011;108:8021-5.
36. Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 2002;22:3251-61.
37. Turner CA, Gula EL, Taylor LP, Watson SJ, Akil H. Antidepressant-like effects of intracerebroventricular FGF2 in rats. Brain Res 2008;1224:63-8.
38. Peruga I, Hartwig S, Merkler D, Thöne J, Hovemann B, Juckel G, *et al.* Endogenous ciliary neurotrophic factor modulates anxiety and depressive-like behavior. Behav Brain Res 2012;229:325-32.
39. Yang P, Arnold SA, Habas A, Hetman M, Hagg T. Ciliary neurotrophic factor mediates dopamine D2 receptor-induced CNS neurogenesis in adult mice. J Neurosci 2008;28:2231-41.
40. Emsley JG, Hagg T. Endogenous and exogenous ciliary neurotrophic factor enhances forebrain neurogenesis in adult mice. Exp Neurol 2003;183:298-310.
41. Dutta R, McDonough J, Chang A, Swamy L, Siu A, Kidd GJ, *et al.* Activation of the ciliary neurotrophic factor (CNTF) signalling pathway in cortical neurons of multiple sclerosis patients. Brain 2007;130:2566-76.
42. Emerich DF, Thanos CG, Sanberg PR. Intraventricular implant of encapsulated CNTF-secreting fibroblasts ameliorates motor deficits in aged rats. Curr Aging Sci 2008;1:105-11.
43. Ichiba M, Nakajima K, Yamanaka Y, Kiuchi N, Hirano T. Autoregulation of the stat3 gene through cooperation with a cAMP-responsive element-binding protein. J Biol Chem 1998;273:6132-8.

44. He F, Ge W, Martinowich K, Becker-Catania S, Coskun V, Zhu W, *et al.* A positive autoregulatory loop of jak-STAT signaling controls the onset of astrogliogenesis. Nat Neurosci 2005;8:616-25.
45. Gutiérrez-Fernández M, Rodríguez-Frutos B, Ramos-Cejudo J, Teresa Vallejo-Cremades M, Fuentes B, Cerdán S, *et al.* Effects of intravenous administration of allogenic bone marrow – And adipose tissue-derived mesenchymal stem cells on functional recovery and brain repair markers in experimental ischemic stroke. Stem Cell Res Ther 2013;4:11.
46. Gutiérrez-Fernández M, Rodríguez-Frutos B, Alvarez-Grech J, Vallejo-Cremades MT, Expósito-Alcaide M, Merino J, *et al.* Functional recovery after hematic administration of allogenic mesenchymal stem cells in acute ischemic stroke in rats. Neuroscience 2011;175:394-405.
47. Huang AH, Snyder BR, Cheng PH, Chan AW. Putative dental pulp-derived stem/stromal cells promote proliferation and differentiation of endogenous neural cells in the hippocampus of mice. Stem cells (Dayton, Ohio) 2008;26:2654-63.
48. Ding J, He Z, Ruan J, Ma Z, Liu Y, Gong C, *et al.* Role of ciliary neurotrophic factor in the proliferation and differentiation of neural stem cells. J Alzheimers Dis 2013;37:587-92.
49. Ceccariglia S, D'altocolle A, Del Fa' A, Silvestrini A, Barba M, Pizzolante F, *et al.* Increased expression of aquaporin 4 in the rat hippocampus and cortex during trimethyltin-induced neurodegeneration. Neuroscience 2014;274:273-88.
50. Greene J, Banasr M, Lee B, Warner-Schmidt J, Duman RS. Vascular endothelial growth factor signaling is required for the behavioral actions of antidepressant treatment: Pharmacological and cellular characterization. Neuropsychopharmacology 2009;34:2459-68.
51. Lang UE, Borgwardt S. Molecular mechanisms of depression: Perspectives on new treatment strategies. Cell Physiol Biochem 2013;31:761-77.
52. Serafini G, Hayley S, Pompili M, Dwivedi Y, Brahmachari G, Girardi P, *et al.* Hippocampal neurogenesis, neurotrophic factors and depression: Possible therapeutic targets? CNS Neurol Disord Drug Targets 2014;13:1708-21.