Review Article | Published: 30 January 2019

Exosomes — beyond stem cells for restorative therapy in stroke and neurological injury

Zheng Gang Zhang, Benjamin Buller & Michael Chopp

Nature Reviews Neurology **15**, 193–203 (2019)

Abstract

Stroke is a leading cause of disability worldwide, and brain injuries devastate patients and their families, but currently no drugs on the market promote neurological recovery. Limited spontaneous recovery of function as a result of brain remodelling after stroke or injury does occur, and cell-based therapies have been used to promote these endogenous processes. Increasing evidence is demonstrating that the positive effects of such cell-based therapy are mediated by exosomes released from the administered cells and that the microRNA cargo in these exosomes is largely responsible for the therapeutic effects. This evidence raises the possibility that isolated exosomes could be used alone as a neurorestorative therapy and that these exosomes could be tailored to maximize clinical benefit. The potential of exosomes as a therapy for brain disorders is therefore being actively investigated. In this Review, we discuss the current knowledge of exosomes and advances in our knowledge of their effects on endogenous neurovascular remodelling events. We also consider the opportunities for exosome-based approaches to therapeutic amplification of brain repair and improvement of recovery after stroke, traumatic brain injury and other diseases in which neurorestoration could be a viable treatment strategy.

Key points

- Exosomes are involved in many aspects of normal brain physiology and facilitate communication between brain cells and between the brain and the periphery.

- Increasing evidence suggests that exosomes from mesenchymal stromal cells (MSCs) mediate the beneficial effects of cell therapy for stroke and traumatic brain injury (TBI).

- The effects of MSC-derived exosomes alone have the potential to improve neurological outcomes in animal models of stroke, TBI and other neurological diseases.

- Of the cargo in exosomes, microRNA (miRNA) is of prime importance in mediating the therapeutic effects.

- Compared with naive MSC-derived exosomes, engineered MSC-derived exosomes that contain selected miRNA have more potent therapeutic effects in stroke and TBIs.

Access options

References

1. Lackland, D. T. et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke* **45**, 315–353 (2014).

2. Duncan, P. W., Goldstein, L. B., Matchar, D., Divine, G. W. & Feussner, J. Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. *Stroke* **23**, 1084–1089 (1992).

3. Ueno, Y. et al. Axonal outgrowth and dendritic plasticity in the cortical peri-infarct area after experimental stroke. *Stroke* **43**, 2221–2228 (2012).

4. Zhang, Z. G. & Chopp, M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. *Lancet Neurol.* **8**, 491–500 (2009).

5. Li, Y., Liu, Z., Xin, H. & Chopp, M. The role of astrocytes in mediating exogenous cell-based restorative therapy for stroke. *Glia* **62**, 1–16 (2014).

6. Chen, J. et al. Therapeutic benefit of intracerebral transplantation of bone marrow stromal cells after cerebral ischemia in rats. *J. Neurol. Sci.* **189**, 49–57 (2001).

7. Chen, J. et al. Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. *Stroke* **32**, 1005–1011 (2001).

8. Chopp, M. & Li, Y. Treatment of neural injury with marrow stromal cells. *Lancet Neurol.* **1**, 92–100 (2002).

9. Zhang, Y. et al. Effect of exosomes derived from multipluripotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain

injury. *J. Neurosurgery* **122**, 856–867 (2015).

10. Moskowitz, M. A., Lo, E. H. & Iadecola, C. The science of stroke: mechanisms in search of treatments. *Neuron* **67**, 181–198 (2010).

11. Xin, H. et al. MiR-133b promotes neural plasticity and functional recovery after treatment of stroke with multipotent mesenchymal stromal cells in rats via transfer of exosome-enriched extracellular particles. *Stem Cells* **31**, 2737–2746 (2013).

12. Xin, H. et al. Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. *J. Cereb. Blood Flow Metab.* **33**, 1711–1715 (2013).

13. Rak, J. Extracellular vesicles — biomarkers and effectors of the cellular interactome in cancer. *Front. Pharmacol.* **4**, 21 (2013).

14. Lener, T. et al. Applying extracellular vesicles based therapeutics in clinical trials — an ISEV position paper. *J. Extracell. Vesicles* **4**, 30087 (2015).

15. Lai, C. P. & Breakefield, X. O. Role of exosomes/microvesicles in the nervous system and use in emerging therapies. *Front. Physiol.* **3**, 228 (2012).

16. Maas, S. L., Breakefield, X. O. & Weaver, A. M. Extracellular vesicles: unique intercellular delivery vehicles. *Trends Cell Biol.* **27**, 172–188 (2017).

17. Mateescu, B. et al. Obstacles and opportunities in the functional analysis of extracellular vesicle RNA — an ISEV position paper. *J. Extracell. Vesicles* **6**, 1286095 (2017).

18. Rufino-Ramos, D. et al. Extracellular vesicles: novel promising delivery systems for therapy of brain diseases. *J. Control. Release* **262**, 247–258 (2017).

19. Park, J. E. et al. Hypoxic tumor cell modulates its microenvironment to enhance angiogenic and metastatic potential by secretion of proteins and exosomes. *Mol. Cell. Proteomics* **9**, 1085–1099 (2010).

20. Kowal, J. et al. Proteomic comparison defines novel markers to characterize heterogeneous populations of extracellular vesicle subtypes. *Proc. Natl Acad. Sci. USA* **113**, E968–E977 (2016).

21. Mantel, P. Y. et al. Infected erythrocyte-derived extracellular vesicles alter vascular function via regulatory Ago2-miRNA complexes in malaria. *Nat. Commun.* **7**, 12727 (2016).

22. Eacker, S. M., Dawson, T. M. & Dawson, V. L. Understanding microRNAs in neurodegeneration. *Nat. Rev. Neurosci.* **10**, 837–841 (2009).

23. Macfarlane, L. A. & Murphy, P. R. MicroRNA: biogenesis, function and role in cancer. *Curr. Genomics* **11**, 537–561 (2010).

24. Meister, G. Argonaute proteins: functional insights and emerging roles. *Nat. Rev. Genet.* **14**, 447–459 (2013).

25. Sempere, L. F., Cole, C. N., McPeek, M. A. & Peterson, K. J. The phylogenetic distribution of metazoan microRNAs: insights into evolutionary complexity and constraint. *J. Exp. Zool. B* **306**, 575–588 (2006).

26. Heimberg, A. M., Sempere, L. F., Moy, V. N., Donoghue, P. C. & Peterson, K. J. MicroRNAs and the advent of vertebrate morphological complexity. *Proc. Natl Acad. Sci. USA* **105**, 2946–2950 (2008).

27. Borroto-Escuela, D. O. et al. The role of transmitter diffusion and flow versus extracellular vesicles in volume transmission in the brain neural-glial networks. *Phil. Trans. R. Soc. B* **370**, 20140183 (2015).

28. Banigan, M. G. et al. Differential expression of exosomal microRNAs in prefrontal cortices of schizophrenia and bipolar disorder patients. *PLOS ONE* **8**, e48814 (2013).

29. Basso, M. & Bonetto, V. Extracellular vesicles and a novel form of communication in the brain. *Front. Neurosci.* **10**, 127 (2016).

30. Holm, M. M., Kaiser, J. & Schwab, M. E. Extracellular vesicles: multimodal envoys in neural maintenance and repair. *Trends Neurosci.* **41**, 360–372 (2018).

31. Faure, J. et al. Exosomes are released by cultured cortical neurones. *Mol. Cell. Neurosci.* **31**, 642–648 (2006).

32. Lachenal, G. et al. Release of exosomes from differentiated neurons and its regulation by synaptic glutamatergic activity. *Mol. Cell. Neurosci.* **46**, 409–418 (2011).

33. Goldie, B. J. et al. Activity-associated miRNA are packaged in Map1b-enriched exosomes released from depolarized neurons. *Nucleic Acids Res.* **42**, 9195–9208 (2014).

34. Xu, B. et al. Neurons secrete miR-132-containing exosomes to regulate brain vascular integrity. *Cell Res.* **27**, 882–897 (2017).

35. Wang, S. et al. Synapsin I is an oligomannose-carrying glycoprotein, acts as an oligomannose-binding lectin, and promotes neurite outgrowth and neuronal survival when released via glia-derived exosomes. *J. Neurosci.* **31**, 7275–7290 (2011).

36. Kramer-Albers, E. M. et al. Oligodendrocytes secrete exosomes containing major myelin and stress-protective proteins: trophic support for axons? *Proteomics Clin. Appl.* **1**, 1446–1461 (2007).

37. Fruhbeis, C. et al. Neurotransmitter-triggered transfer of exosomes mediates oligodendrocyte-neuron communication. *PLOS Biol.* **11**, e1001604 (2013).

38. Fruhbeis, C., Frohlich, D., Kuo, W. P. & Kramer-Albers, E. M. Extracellular vesicles as mediators of neuron-glia communication. *Front. Cell. Neurosci.* **7**, 182 (2013).

39. Lafourcade, C., Ramirez, J. P., Luarte, A., Fernandez, A. & Wyneken, U. MiRNAs in astrocyte-derived exosomes as possible mediators of neuronal plasticity. *J. Exp. Neurosci.* **10**, 1–9 (2016).

40. Liu, Y. et al. Targeted exosome-mediated delivery of opioid receptor Mu siRNA for the treatment of morphine relapse. *Sci. Rep.* **5**, 17543 (2015).

41. Guitart, K. et al. Improvement of neuronal cell survival by astrocyte-derived exosomes under hypoxic and ischemic conditions depends on prion protein. *Glia* **64**, 896–910 (2016).

42. Luarte, A. et al. Astrocytes at the hub of the stress response: potential modulation of neurogenesis by miRNAs in astrocyte-derived exosomes. *Stem Cells Int.* **2017**, 1719050 (2017).

43. Jovicic, A. & Gitler, A. D. Distinct repertoires of microRNAs present in mouse astrocytes compared to astrocyte-secreted exosomes. *PLOS ONE* **12**, e0171418 (2017).

44. Zhang, Z. G. & Chopp, M. Exosomes in stroke pathogenesis and therapy. *J. Clin. Invest.* **126**, 1190–1197 (2016).

45. Ophelders, D. R. et al. Mesenchymal stromal cell-derived extracellular vesicles protect the fetal brain after hypoxia-ischemia. *Stem Cells Transl Med.* **5**, 754–763 (2016).

46. Doeppner, T. R. et al. Extracellular vesicles improve post-stroke neuroregeneration and prevent postischemic immunosuppression. *Stem Cells Transl Med.* **4**, 1131–1143 (2015).

47. Otero-Ortega, L. et al. White matter repair after extracellular vesicles administration in an experimental animal model of subcortical stroke. *Sci. Rep.* **7**, 44433 (2017).

48. Kim, D. K. et al. Chromatographically isolated CD63+CD81+ extracellular vesicles from mesenchymal stromal cells rescue cognitive impairments after TBI. *Proc. Natl Acad. Sci. USA* **113**, 170–175 (2015).

49. Han, Y. et al. Multipotent mesenchymal stromal cell-derived exosomes improve functional recovery after experimental intracerebral hemorrhage in the rat. *J. Neurosurg.* https://doi.org/10.3171/2018.2.JNS171475 (2018).

50. Otero-Ortega, L. et al. Exosomes promote restoration after an experimental animal model of intracerebral hemorrhage. *J. Cereb. Blood Flow Metab.* **38**, 767–779 (2018).

51. Williams, A. M. et al. Mesenchymal stem cell-derived exosomes provide neuroprotection and improve long-term neurologic outcomes in a swine model of traumatic brain injury and hemorrhagic shock. *J. Neurotrauma* https://doi.org/10.1089/neu.2018.5711 (2018).

52. Buller, B. M. et al. Exosomes from rhesus monkey MSCs promote neuronal growth and myelination. *Stroke* **47** (Suppl. 1), A68 (2016).

53. Orczykowski, M. E. et al. Cell based therapy enhances activation of ventral premotor cortex to improve recovery following primary motor cortex injury. *Exp. Neurol.* **305**, 13–25 (2018).

54. Moore, T. L. et al. Recovery from ischemia in the middle-aged brain: a nonhuman primate model. *Neurobiol. Aging* **33**, 619.e9–619.e24 (2012).

55. Bruhn, H. et al. Non-invasive differentiation of tumors with use of localized 1-H spectroscopy in vivo: initial experience in patients with cerebral tumors. *Invest. Radiol.* **25**, 1047–1050 (1990).

56. Marcus, M. E. & Leonard, J. N. FedExosomes: engineering therapeutic biological nanoparticles that truly deliver. *Pharmaceuticals* **6**, 659–680 (2013).

57. Zhang, Y. et al. Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury. *Neurochem. Int.* **111**, 69–81 (2016).

58. Kordelas, L. et al. MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease. *Leukemia* **28**, 970–973 (2014).

59. Webb, R. L. et al. Human neural stem cell extracellular vesicles improve tissue and functional recovery in the murine thromboembolic stroke model. *Transl Stroke Res.* **9**, 530–539 (2017).

60. Webb, R. L. et al. Human neural stem cell extracellular vesicles improve recovery in a porcine model of ischemic stroke. *Stroke* **49**, 1248–1256 (2018).

61. Xiao, B. et al. Endothelial cell-derived exosomes protect SH-SY5Y nerve cells against ischemia/reperfusion injury. *Int. J. Mol. Med.* **40**, 1201–1209 (2017).

62. Catanese, L., Tarsia, J. & Fisher, M. Acute ischemic stroke therapy overview. *Circ. Res.* **120**, 541–558 (2017).

63. Goyal, M., Hill, M. D., Saver, J. L. & Fisher, M. Challenges and opportunities of endovascular stroke therapy. *Ann. Neurol.* **79**, 11–17 (2016).

64. Fisher, M. & Saver, J. L. Future directions of acute ischaemic stroke therapy. *Lancet Neurol.* **14**, 758–767 (2015).

65. Neuhaus, A. A., Couch, Y., Hadley, G. & Buchan, A. M. Neuroprotection in stroke: the importance of collaboration and reproducibility. *Brain* **140**, 2079–2092 (2017).

66. Saver, J. L. et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA **316**, 1279–1288 (2016).

67. Jadhav, A. P. et al. Eligibility for endovascular trial enrollment in the 6- to 24-hour time window: analysis of a single comprehensive stroke center. *Stroke* **49**, 1015–1017 (2018).

68. Ganesh, A. & Goyal, M. Thrombectomy for acute ischemic stroke: recent insights and future directions. *Curr. Neurol. Neurosci. Rep.* **18**, 59 (2018).

69. Lapchak, P. A., Boitano, P. D., de Couto, G. & Marban, E. Intravenous xenogeneic human cardiosphere-derived cell extracellular vesicles (exosomes) improves behavioral function in small-clot embolized rabbits. *Exp. Neurol.* **307**, 109–117 (2018).

70. Billing, A. M. et al. Comprehensive transcriptomic and proteomic characterization of human mesenchymal stem cells reveals source specific cellular markers. *Sci. Rep.* **6**, 21507 (2016).

71. Walczak, P. et al. Dual-modality monitoring of targeted intraarterial delivery of mesenchymal stem cells after transient ischemia. *Stroke* **39**, 1569–1574 (2008).

72. Herberts, C. A., Kwa, M. S. & Hermsen, H. P. Risk factors in the development of stem cell therapy. *J. Transl Med.* **9**, 29 (2011).

73. Wong, R. S. Mesenchymal stem cells: angels or demons? *J. Biomed. Biotechnol.* **2011**, 459510 (2011).

74. Krupinski, J., Kaluza, J., Kumar, P., Kumar, S. & Wang, J. M. Role of angiogenesis in patients with cerebral ischemic stroke. *Stroke* **25**, 1794–1798 (1994).

75. Jin, K. et al. Evidence for stroke-induced neurogenesis in the human brain. *Proc. Natl Acad. Sci. USA* **103**, 13198–13202 (2006).

76. Macas, J., Nern, C., Plate, K. H. & Momma, S. Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. *J. Neurosci.* **26**, 13114–13119 (2006).

77. Minger, S. L. et al. Endogenous neurogenesis in the human brain following cerebral infarction. *Regen. Med.* **2**, 69–74 (2007).

78. Xin, H., Li, Y. & Chopp, M. Exosomes/miRNAs as mediating cell-based therapy of stroke. *Front. Cell. Neurosci.* **8**, 377 (2014).

79. Xiong, Y., Mahmood, A. & Chopp, M. Emerging potential of exosomes for treatment of traumatic brain injury. *Neural Regen. Res.* **12**, 19–22 (2017).

80. Andras, I. E. & Toborek, M. Extracellular vesicles of the blood-brain barrier. *Tissue Barriers* **4**, e1131804 (2016).

81. Grange, C. et al. Biodistribution of mesenchymal stem cell-derived extracellular vesicles in a model of acute kidney injury monitored by optical imaging. *Int. J. Mol. Med.* **33**, 1055–1063 (2014).

82. Di Rocco, G., Baldari, S. & Toietta, G. Towards therapeutic delivery of extracellular vesicles: strategies for in vivo tracking and biodistribution analysis. *Stem Cells Int.* **2016**, 5029619 (2016).

83. Betzer, O. et al. In vivo neuroimaging of exosomes using gold nanoparticles. *ACS Nano* **11**, 10883–10893 (2017).

84. Hwang, D. W. et al. Noninvasive imaging of radiolabeled exosome-mimetic nanovesicle using (99m)Tc-HMPAO. *Sci. Rep.* **5**, 15636 (2015).

85. Yuan, D. et al. Macrophage exosomes as natural nanocarriers for protein delivery to inflamed brain. *Biomaterials* **142**, 1–12 (2017).

86. Zhang, Y. et al. Exosomes derived from mesenchymal stromal cells promote axonal growth of cortical neurons. *Mol. Neurobiol.* **54**, 2659–2673 (2017).

87. Tassew, N. G. et al. Exosomes mediate mobilization of autocrine Wnt10b to promote axonal regeneration in the injured CNS. *Cell Rep.* **20**, 99–111 (2017).

88. Haqqani, A. S. et al. Method for isolation and molecular characterization of extracellular microvesicles released from brain endothelial cells. *Fluids Barriers CNS* **10**, 4 (2013).

89. Pan, W. et al. Exosomes derived from ischemic cerebral endothelial cells and neural progenitor cells enhance neurogenesis and angiogenesis. *Stroke* **47** (Suppl. 1), AWMP39 (2016).

90. Zhang, Y. et al. Hypothalamic stem cells control ageing speed partly through exosomal miRNAs. *Nature* **548**, 52–57 (2017).

91. Andras, I. E. et al. Extracellular vesicles of the blood-brain barrier: role in the HIV-1 associated amyloid beta pathology. *Mol. Cell. Neurosci.* **79**, 12–22 (2017).

92. Xin, H. et al. Secondary release of exosomes from astrocytes contributes to the increase in neural plasticity and improvement of functional recovery after stroke in rats treated with exosomes harvested from microRNA 133b-overexpressing multipotent mesenchymal stromal cells. *Cell Transplant.* **26**, 243–257 (2017).

93. Couch, Y. et al. Inflammatory stroke extracellular vesicles induce macrophage activation. *Stroke* **48**, 2292–2296 (2017).

94. Esenwa, C. C. & Elkind, M. S. Inflammatory risk factors, biomarkers and associated therapy in ischaemic stroke. *Nat. Rev. Neurol.* **12**, 594–604 (2016).

95. Drommelschmidt, K. et al. Mesenchymal stem cell-derived extracellular vesicles ameliorate inflammation-induced preterm brain injury. *Brain Behav. Immun.* **60**, 220–232 (2017).

96. Cui, G. H. et al. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. *FASEB J.* **32**, 654–668 (2017).

97. Chen, J. et al. MiR-126 affects brain-heart interaction after cerebral ischemic stroke. *Transl Stroke Res.* **8**, 374–385 (2017).

98. Balusu, S. et al. Identification of a novel mechanism of blood-brain communication during peripheral inflammation via choroid plexus-derived extracellular vesicles. *EMBO Mol. Med.* **8**, 1162–1183 (2016).

99. Chopp, M. & Zhang, Z. G. Emerging potential of exosomes and noncoding microRNAs for the treatment of neurological injury/diseases. *Expert Opin. Emerg. Drugs* **20**, 523–526 (2015).

100. van Niel, G., D'Angelo, G. & Raposo, G. Shedding light on the cell biology of extracellular vesicles. *Nat. Rev. Mol. Cell Biol.* **19**, 213–228 (2018).

101. Guduric-Fuchs, J. et al. Selective extracellular vesicle-mediated export of an overlapping set of microRNAs from multiple cell types. *BMC Genomics* **13**, 357 (2012).

102. Melo, S. A. et al. Cancer exosomes perform cell-independent microRNA biogenesis and promote tumorigenesis. *Cancer Cell* **26**, 707–721 (2014).

103. Collino, F. et al. AKI recovery induced by mesenchymal stromal cell-derived extracellular vesicles carrying microRNAs. *J. Am. Soc. Nephrol.* **26**, 2349–2360 (2015).

104. Zhang, R. L. et al. Cerebral endothelial derived exosomes abolish cognitive impairment induced by ablation of Dicer in adult neural stem cells. *Stroke* **48** (Suppl. 1), AWMP48 (2017).

105. Mead, B. & Tomarev, S. Bone marrow-derived mesenchymal stem cells-derived exosomes promote survival of retinal ganglion cells through miRNA-dependent mechanisms. *Stem Cells Transl Med.* **6**, 1273–1285 (2017).

106. Katsuda, T., Oki, K. & Ochiya, T. Potential application of extracellular vesicles of human adipose tissue-derived mesenchymal stem cells in Alzheimer's disease therapeutics. *Methods Mol. Biol.* **1212**, 171–181 (2015).

107. Xin, H. et al. Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. *Stem Cells* **30**, 1556–1564 (2012).

108. Nam, J. W. et al. Global analyses of the effect of different cellular contexts on microRNA targeting. *Mol. Cell* **53**, 1031–1043 (2014).

109. He, Z. & Jin, Y. Intrinsic control of axon regeneration. *Neuron* **90**, 437–451 (2016).

110. Zhang, Y. et al. The microRNA-17-92 cluster enhances axonal outgrowth in embryonic cortical neurons. *J. Neurosci.* **33**, 6885–6894 (2013).

111. Jones, E. V. & Bouvier, D. S. Astrocyte-secreted matricellular proteins in CNS remodelling during development and disease. *Neural Plast.* **2014**, 321209 (2014).

112. Edbauer, D. et al. Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132. *Neuron* **65**, 373–384 (2010).

113. Magill, S. T. et al. microRNA-132 regulates dendritic growth and arborization of newborn neurons in the adult hippocampus. *Proc. Natl Acad. Sci. USA* **107**, 20382–20387 (2010).

114. Dozio, V. & Sanchez, J. C. Characterisation of extracellular vesicle-subsets derived from brain endothelial cells and analysis of their protein cargo modulation after TNF exposure. *J. Extracell. Vesicles* **6**, 1302705 (2017).

115. Tkach, M. & Thery, C. Communication by extracellular vesicles: where we are and where we need to go. *Cell* **164**, 1226–1232 (2016).

116. Alvarez-Erviti, L. et al. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat. Biotechnol.* **29**, 341–345 (2011).

117. Kumar, P. et al. Transvascular delivery of small interfering RNA to the central nervous system. *Nature* **448**, 39–43 (2007).

118. Coimbra, J. R. M. et al. Highlights in BACE1 inhibitors for Alzheimer's disease treatment. *Front. Chem.* **6**, 178 (2018).

119. Yang, J., Zhang, X., Chen, X., Wang, L. & Yang, G. Exosome mediated delivery of miR-124 promotes neurogenesis after ischemia. *Mol. Ther. Nucleic Acids* **7**, 278–287 (2017).

120. Gyorgy, B. et al. Rescue of hearing by gene delivery to inner-ear hair cells using exosome-associated AAV. *Mol. Ther.* **25**, 379–391 (2017).

121. Tian, T. et al. Surface functionalized exosomes as targeted drug delivery vehicles for cerebral ischemia therapy. *Biomaterials* **150**, 137–149 (2018).

122. Zhuang, X. et al. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. *Mol. Ther.* **19**, 1769–1779 (2011).

123. Kalani, A. et al. Curcumin-loaded embryonic stem cell exosomes restored neurovascular unit following ischemia-reperfusion injury. *Int. J. Biochem. Cell Biol.* **79**, 360–369 (2016).

124. Xin, H. et al. MicroRNA cluster miR-17-92 cluster in exosomes enhance neuroplasticity and functional recovery after stroke in rats. *Stroke* **48**, 747–753 (2017).

125. Shen, H. et al. Role of exosomes derived from miR-133b modified MSCs in an experimental rat model of intracerebral hemorrhage. *J. Mol. Neurosci.* **64**, 421–430 (2018).

126. Sterzenbach, U. et al. Engineered exosomes as vehicles for biologically active proteins. *Mol. Ther.* **25**, 1269–1278 (2017).

127. Long, Q. et al. Intranasal MSC-derived A1-exosomes ease inflammation, and prevent abnormal neurogenesis and memory dysfunction after status epilepticus. *Proc. Natl Acad. Sci. USA* **114**, E3536–E3545 (2017).

128. Haney, M. J. et al. Exosomes as drug delivery vehicles for Parkinson's disease therapy. *J. Control. Release* **207**, 18–30 (2015).

129. Pachler, K. et al. A Good Manufacturing Practice-grade standard protocol for exclusively human mesenchymal stromal cell-derived extracellular vesicles. *Cytotherapy* **19**, 458–472 (2017).

130. Gimona, M., Pachler, K., Laner-Plamberger, S., Schallmoser, K. & Rohde, E. Manufacturing of human extracellular vesicle-based therapeutics for clinical use. *Int. J. Mol. Sci.* **18**, E1190 (2017).

131. Frank, J. et al. Extracellular vesicles protect glucuronidase model enzymes during freeze-drying. *Sci. Rep.* **8**, 12377 (2018).

132. Pachler, K. et al. An in vitro potency assay for monitoring the immunomodulatory potential of stromal cell-derived extracellular vesicles. *Int. J. Mol. Sci.* **18**, E1413 (2017).

133. Reiner, A. T. et al. Concise review: developing best-practice models for the therapeutic use of extracellular vesicles. *Stem Cells Transl Med.* **6**, 1730–1739 (2017).

134. Cunningham, C. J., Redondo-Castro, E. & Allan, S. M. The therapeutic potential of the mesenchymal stem cell secretome in ischaemic stroke. *J. Cereb. Blood Flow Metab.* **38**, 1276–1292 (2018).

135. Anderson, J. D. et al. Comprehensive proteomic analysis of mesenchymal stem cell exosomes reveals modulation of angiogenesis via nuclear factor-kappaB signaling. *Stem Cells* **34**, 601–613 (2016).

Acknowledgements

The authors acknowledge support from US NIH grants R01 NS 088656 (M.C.) and RO1 NS075156 (Z.G.Z.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Author information

Affiliations

Department of Neurology, Henry Ford Hospital, Detroit, MI, USA
Zheng Gang Zhang, Benjamin Buller & Michael Chopp

Department of Physics, Oakland University, Rochester, MI, USA

Michael Chopp

Contributions

Z.G.Z. and B.B. researched data for the article. All authors made substantial contributions to discussion of content, contributed to writing of the article and reviewed and edited the manuscript before submission.

Corresponding author

Correspondence to Zheng Gang Zhang.

Ethics declarations

Competing interests

The authors declare no competing interests.

Additional information

Publisher's note

Related links

US National Library of Medicine Clinical Trials: http://www.clinicaltrials.gov

Rights and permissions

About this article

Published **Issue Date** **DOI**
30 January 2019 April 2019 https://doi.org/10.1038/s41582-018-0126-4

Subjects Brain injuries • Regeneration and repair in the nervous system • Stroke • Therapeutics

Further reading

MicroRNAs and Regeneration in Animal Models of CNS Disorders -
https://doi.org/10.1007/s11064-019-02777-6
Tamara Roitbak

Neurochemical Research (2019)

Nature Reviews Neurology

ISSN 1759-4766 (online)