Taylor & Francis
Taylor & Francis Group

Journal of Investigative Surgery

ISSN: 0894-1939 (Print) 1521-0553 (Online) Journal homepage: https://www.tandfonline.com/loi/iivs20

Different Roles Played by Adipose-Derived Stem Cells in Peripheral Nerve Regeneration: State of the Art

Francesco Ruben Giardino, Roberto Cuomo, Giuseppe Nisi, Cesare Brandi & Luca Grimaldi

To cite this article: Francesco Ruben Giardino, Roberto Cuomo, Giuseppe Nisi, Cesare Brandi & Luca Grimaldi (2019): Different Roles Played by Adipose-Derived Stem Cells in Peripheral Nerve Regeneration: State of the Art, Journal of Investigative Surgery, DOI: 10.1080/08941939.2019.1671559

To link to this article: https://doi.org/10.1080/08941939.2019.1671559

Published online: 06 Oct 2019.

Journal of Investigative Surgery, 0: 1–2, 2019

ISSN: 0894-1939 print / 1521-0553 online
DOI: 10.1080/08941939.2019.1671559

Taylor & Francis
Taylor & Francis Group

COMMENTARY

Different Roles Played by Adipose-Derived Stem Cells in Peripheral Nerve Regeneration: State of the Art

Francesco Ruben Giardino, Roberto Cuomo, Giuseppe Nisi, Cesare Brandi, Luca Grimaldi

Unit of Plastic and Reconstructive Surgery, S. Maria Alle Scotte Hospital, University of Siena, Siena, Italy

Peripheral nerve injury is commonly attributable to traffic and industrial accidents, natural disasters, and war damage. Destruction of nerve fibers results in denervation of targeted muscles, which undergo progressive loss of function and atrophy as well: these conditions follow account for nearly $150 billion in annual health care spending in the United States [1,2].

A recent original article shows that Polyethylene Glycol (PEG) improves results of peripheral nerve microsuturing, with no need of Bittner's protocol.

This interesting, perspective, experimental study focused on regeneration of sciatic nerve, and on the PEG's role in enhancing sciatic nerve restoration after PNI, resulting into histologically demonstrated prevention of Wallerian degeneration, partial prevention of muscular atrophy and acceleration of recovery after sharp transections.

Behavioral assessment included both sensory feedback and motion control (Sciatic Function Index), with significant clinical improvement, while in vivo electrophysiology, involving the recording of compound muscle action potentials of the gastrocnemius muscle, showed higher peak values in rats treated with PEG compared to those in which standard sutures without PEG were performed. Last but not least, the authors focuses on the importance of building and enhancing a "pro-regenerative microenvironment" in order to concentrate specific tissue growth factors in damaged tissues, which can currently be considered a hot topic in regenerative surgery [3].

Different therapeutic approaches have been proposed for PNI, such as micro-sutures, synthetic or autologous conduits and autologous nerve grafts, which is preferred in short gaps injuries [4]. However, new strategies and research fields are debated about nervous tissue regeneration. Experimental studies published during last years show an increase of interest on Adipose derived stem cells (ASCs) in many fields, mainly because they can be easily harvested and have multilineage differentiation potential, can undergo effective expansion within weeks, can be obtained in a noninvasive manner and currently accesible at the point-of-care due to significant technological development.

The use of different heterologous substances or materials (such as PEG) in peripheral nerve regeneration have been proposed, and, moreover, as supports for ASCs action: in a recent study has been demonstrated the efficacy of polycaprolactone (PCL) with addition of adipose stem in repairing a 6 mm surgically ablated peripheral nerve, through mechanism wich are still not clear, but an increase in levels of S100 (Schwann cell marker) expression was observed [5].

It has been demonstrated as well that the ASC-Exosomes (small membrane vesicles with a diameter of 50–150 nm) significantly improve peripheral nerve regeneration via optimizing Schwann Cells function and thereby represent an effective perspective in nerve tissue engineering [6]. It seems that implanted ASCs could improve the microenvironment of ANA (acellular nerve allograft) through secretion of neurotrophins and growth factors such as NGF (Nerve Growth Factor), BDNF (Brain-derived neurotrophic factor), CNTF (Ciliary neurotrophic factor), GDNF (glial-derived neurotrophic factor), and TGF-β that can induce axonal elongation. The genes of NGF, GDNF, and BDNF were persistently expressed after integrating neural differentiated ADSCs into ANM [7].

Other data demonstrated that the systemic administration of ALCAR (acetyl-l-carnitine) enhanced ASC-transplanted nerve allograft regenerative properties and resulting peripheral nerve

Received 16 September 2019; accepted 19 September 2019.
Address correspondence to Unit of Plastic and Reconstructive Surgery, S. Maria Alle Scotte Hospital, University of Siena, Mario Bracci Street, Siena (SI), 53100, Italy. E-mail. f.ruben.giardino@gmail.com

regeneration which, again, according to another study, seems related to an interaction between ASCs, regenerative axons (Schwann Cells) and the ability to secrete neurotrophic factors (such as NGF, GDNF, and BDNF) [8].

About muscular atrophy, an investigation is suggestive that an ASC injection into denervated muscle post-operatively is able to delay the onset of atrophy [9].

Beside, recent rodent studies have shown that ASCs promote muscle mass retention after PNI when administered into the denervated muscle [10,11].

However, alongside these enormous advantages about effects of ASCs on PNI in enhancing a good microenvironment for nervous tissue regeneration (any reconstructive surgical technique is used), producing growth factors and stimulating Schwann cells proliferation and their relative ease of use, some concern still remains. The low survival rate and retention of transplanted ASCs limits their therapeutic potential [12] and the harmful microenvironment of injured tissues makes ASCs survival difficult, whereas oxidative stress, energy failure and inflammatory response can lead to apoptosis [13]. Therefore, any approach that enhances survival and retention capacity of ASCs may improve the nerve regeneration process and be consequential to functional recovery.

Finally, safety in the use of stem-cells therapies is still a huge and debated argument in literature, and an univocal consent on their clinical applications, treatments and harvesting is currently not available, not least due to the differences in stem-cells regulations between various countries.

Further experimental studies are needed to better understand the molecular and cellular mechanisms induced by the use of stem cells in PNI, and, in order to propose their systematic use as adjuvants of different surgical techniques, standardization of therapeutic protocols and materials used in peripheral nerve repair is required.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

REFERENCES

[1] Grinsell D, Keating CP. Peripheral nerve reconstruction after injury: a review of clinical and experimental therapies. *Biomed Res Int*. 2014;2014:1.

[2] Robinson LR. Traumatic injury to peripheral nerves. *Muscle Nerve*. 2000;23(6):863–873. doi:10.1002/(SICI)1097-4598(200006)23:6<863::AID-MUS4>3.0.CO;2-0.

[3] Zhao X, Li B, Guan X, et al. Peg-enhanced behavioral recovery after sciatic nerve transection and either suturing or sleeve conduit deployment in rats. [published online ahead of print August 23, 2019]. *J Invest Surg*. doi:10.1080/08941939.2019.1654047

[4] Faroni A, Mobasseri SA, Kingham PJ, et al. Peripheral nerve regeneration: experimental strategies and future perspectives. *Adv Drug Deliv Rev*. 2015;82–83:160–167. doi:10.1016/j.addr.2014.11.010.

[5] Passipieri JA, Dienes J, Frank J, et al. Adipose stem cells enhance nerve regeneration and muscle function in a peroneal nerve ablation model. *Tissue Eng Part A*. 2019. doi:10.1089/ten.TEA.2018.0244. [Epub ahead of print]

[6] Chen J, Ren S, Duscher D, et al. J Exosomes from human adipose-derived stem cells promote sciatic nerve regeneration via optimizing Schwann cell function. *J Cell Physiol*. 2019;234(12):23097–23110. doi:10.1002/jcp.28873.

[7] Zhang Y, Luo H, Zhang Z, et al. A nerve graft constructed with xenogeneic acellular nerve matrix and autologous adipose-derived mesenchymal stem cells. *Biomaterials*. 2010;31(20):5312–5324. doi:10.1016/j.biomaterials.2010.03.029.

[8] Mohammad-Bagher G, Arash A, Morteza BR, et al. Synergistic effects of acetyl-l-carnitine and adipose-derived stromal cells on improving regenerative capacity of acellular nerve allograft in sciatic nerve defect. *J Pharmacol Exp Ther*. 2019;368(3):490–502. Erratum in: J Pharmacol Exp Ther. 2019;369(1):181. doi:10.1124/jpet.118.254540.

[9] Schilling BK, Schusterman MA, Kim DY, et al. Adipose-derived stem cells delay muscle atrophy after peripheral nerve injury in the rodent model. *J Pharmacol Exp Ther*. 2019;368(3):490–502. doi:10.1124/jpet.118.254540.

[10] Park JU, Kwon ST. Potential of autologous adipose-derived stem cells to regenerate atrophied muscle in a rat model. *Wound Rep and Reg*. 2017;25(6):944–955. doi:10.1111/wrr.12598.

[11] Schaakxs D, Kalbermatten DF, Raffoul W, et al. Regenerative cell injection in denervated muscle reduces atrophy and enhances recovery following nerve repair. *Muscle Nerve*. 2013;47(5):691–701. doi:10.1002/mus.23662.

[12] Potier E, Ferreira E, Meunier A, et al. Prolonged hypoxia concomitant with serum deprivation induces massive human mesenchymal stem cell death. *Tissue Eng*. 2007;13(6):1325–1331. doi:10.1089/ten.2006.0325.

[13] Toma C, Pittenger MF, Cahill KS, et al. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation*. 2002;105(1):93–98. doi:10.1161/hc0102.101442.