Journal of Neurology, Neurosurgery and Spine

Editorial
Published: 16 Mar, 2017

Replacement Cells for CNS Repair: New Tools for Neurology & Neurosurgery

*McKinnon RD**

Department of Surgery (Neurosurgery), Rutgers -Robert Wood Johnson Medical School, USA

Keywords

Central nervous system (CNS); CNS repair; Therapeutic strategies; Neuro-degeneration

Editorial

The central nervous system (CNS) does not self repair and our expanding geriatric population needs novel therapeutic strategies to repair accumulating damage from injury, degeneration and disease. Two issues that prevent CNS self repair are the inability to replace lost neurons and glia, and the failure of surviving neurons to extend new axons through damaged tissue. The failure to rewire is largely due to inhibitory factors in the astroglial scar and in the myelin sheaths that are generated during neural development. Myelin insulates axons for fast conduction and also suppresses axon sprouting, thus preventing inappropriate *de novo* rewiring. This suppression comes at a cost such as the inability to re-grow axons through a spinal cord injury. Thus the damaged CNS relies on surviving circuits to compensate for lost function. The inability to replace lost cells likely represents a lack of stem cell resources, rather than repair competence, since glial cell transplants can promote functional recovery in pre-clinical studies [1]. There are exceptions, such as neurogenesis in the adult olfactory bulb and hippocampus. However, for the majority of the CNS, cell replacement is inadequate. This may be a consequence of the rewiring flaw since there is little use for replacement cells that cannot make functional connections. Thus any strategy for CNS repair must address both cell replacement and axonal rewiring issues. Here I discuss current issues involved in cell therapy strategies including the perils of exogenous cell replacement (cell transplants) and the emerging potential of endogenous cell recruitment (direct cell reprogramming) for repair of the damaged CNS.

OPEN ACCESS

Correspondence:
Randall D McKinnon, Department of Surgery (Neurosurgery), Rutgers -Robert Wood Johnson Medical School, 675 Hoes Lane, R309, Piscataway NJ 08854 USA, Tel: 7322354419; E-mail: mckinnon@rwjms.rutgers.edu

Received Date: *04 Mar 2017*
Accepted Date: *14 Mar 2017*
Published Date: *16 Mar 2017*

Citation:
McKinnon RD. Replacement Cells for CNS Repair: New Tools for Neurology & Neurosurgery. J Neurol Neurosurg Spine. 2017; 2(1): 1009.

Exogenous Replacement Cells

Three potential sources of replacement cells for brain repair include grafts of fetal brain tissue, grafts derived from pluripotent embryonic stem cells (ESCs), and cells generated *in vitro* by reprogramming patient-specific somatic cells such as dermal fibroblasts. Fetal brain grafts were used in the first placebo-controlled neurosurgical trial in the USA, to replace dopaminergic neurons lost in Parkinson's disease; the fetal tissue proved both difficult to standardize and ineffective. ESC-derived cells [2] were first used in a trial for acute spinal cord injury, based on pre-clinical studies with glial (oligodendrocyte progenitor) cell transplants [3]; the trial was halted early principally due to costs. Both of these graft sources require donor tissue and thus have ethical limitations, and both represent allografts where the required immune suppression has serious side effects. In addition, ESC-derived grafts carry a risk for neoplasia. Our pre-clinical studies demonstrated that therapeutic engraftment requires cell numbers that easily approach the neoplastic load of such cultures [4,5], and we believe pluripotent ESC-derived grafts may never be considered therapeutically safe for organ repair.

The third source of replacement cells can be generated by genetic engineering to Trans-differentiate ("reprogram") somatic cells into functional neurons or glia [6]. Cell reprogramming represents a novel strategy to generate patient-specific (and thus ethically neutral) autologous replacement cells. Yamanaka identified nuclear transcription factors that reprogram fibroblasts into induced pluripotent stem (iPS) cells [7], and these can subsequently be re-differentiated into neurons or glial cells in the same way as ESCs. However iPS-derived autologous grafts also have neoplastic potential and since they are immune privileged they present an even greater concern than ESC-derived allografts. An emerging alternative is to avoid pluripotent intermediates and directly reprogram somatic cells into the desired cell types. Yamanaka's work fueled the studies that now demonstrate direct reprogramming of pancreatic exocrine cells into β-cells [8] and somatic

fibroblasts into hepatocytes, cardiomyocytes, blood progenitors and neurons [9-16]. These advances give much hope to the possibility of direct reprogramming to generate CNS replacement cells.

There remain significant limitations to the utility of exogenously reprogrammed cells for brain repair. Since the underlying mechanism is not yet elucidated, it is not clear whether such cells will be stable and functional. The current efficiency of reprogramming (0.1%) is also very low and the few graftable cells generated require extensive mitogen amplification *in vitro* which raises concerns for both quality control and karyotype stability. Chromatin remodeling factors may provide the key to increasing the reprogramming efficiency. Chromatin remodeling is an early event [17] and a limiting factor [18], and small molecules that remodel the epigenome enhance iPS cell reprogramming [19,20]. This area of study will undoubtedly have a tremendous impact on the utility of direct reprogramming for cell therapeutics.

Endogenous Replacement - Direct Reprogramming *In Vivo*

An emerging strategy to avoid long term culture of graft cells is to directly reprogram target cells within the CNS [21]. For *in vivo* reprogramming to work it is necessary to identify both target cells and transgene delivery strategies to introduce the appropriate transcription factors. To date pericytes [16] and astrocytes [22,23] can be reprogrammed into induced neurons, and satellite glia have been reprogrammed into myelinating glia [24]. Another potential target population is NG2 glial cells which represent 5% of the cells in the adult brain [25]. While viral vectors are feasible, gene transduction using episomal plasmids would avoid the safety concerns of viral vectors. Finally, while many of these studies focus on neuronal replacement, the regeneration of myelin forming oligodendrocytes may be a better focus for proof of concept since these cells do not require long distance rewiring to generate functional connections.

Acknowledgment

Supported by grants from the New Jersey Commission on Spinal Cord Research (11-0015-SCR).

References

1. Chen CP, Kiel ME, Sadowski D, McKinnon RD. From stem cells to oligodendrocytes: Prospects for brain therapy. Stem Cell Rev. 2007; 3: 280-288.
2. Murry CE, Keller G. Differentiation of embryonic stem cells to clinically relevant populations: Lessons from embryonic development. Cell. 2008; 132: 661-680.
3. Keirstead HS, Nistor G, Bernal G, Totoiu M, Cloutier F, Sharp K, et al. Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. J Neurosci. 2005; 25: 4694-4705.
4. Kiel ME, Chen CP, Sadowski D, McKinnon RD. Stem cell-derived therapeutic myelin repair requires 7% cell replacement. Stem Cells. 2008; 26: 2229-2236.
5. Sadowski D, Kiel ME, Apicella M, Arriola AG, Chen CP, McKinnon RD. Teratogenic Potential in Cultures Optimized for Oligodendrocyte Development from Mouse Embryonic Stem Cells. Stem Cells Dev. 2010; 19: 1343-1353.
6. Amamoto R, Arlotta P. Development-inspired reprogramming of the mammalian central nervous system. Science. 2014; 343: 1239882.
7. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006; 126: 663-676.
8. Zhou Q, Brown J, Kanarek A, Rajagopal J, Melton DA. *In vivo* reprogramming of adult pancreatic exocrine cells to beta-cells. Nature. 2008; 455: 627-632.
9. Szabo E, Rampalli S, Risueno RM, Schnerch A, Mitchell R, Fiebig-Comyn A, et al. Direct conversion of human fibroblasts to multilineage blood progenitors. Nature. 2010; 468: 521-526.
10. Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, et al. Direct Reprogramming of Fibroblasts into Functional Cardiomyocytes by Defined Factors. Cell. 2010; 142: 375-386.
11. Vierbuchen T, Ostermeier A, Pang ZP, Kokubu Y, Sudhof TC, Wernig M. Direct conversion of fibroblasts to functional neurons by defined factors. Nature. 2010; 463: 1035-1041.
12. Efe JA, Hilcove S, Kim J, Zhou H, Ouyang K, Wang G, et al. Conversion of mouse fibroblasts into cardiomyocytes using a direct reprogramming strategy. Nat Cell Biol. 2011; 13: 215-222.
13. Sekiya S, Suzuki A. Direct conversion of mouse fibroblasts to hepatocyte-like cells by defined factors. Nature. 2011; 475: 390-393.
14. Son EY, Ichida JK, Wainger BJ, Toma JS, Rafuse VF, Woolf CJ, et al. Conversion of mouse and human fibroblasts into functional spinal motor neurons. Cell Stem Cell. 2011; 9: 205-218.
15. Pfisterer U, Kirkeby A, Torper O, Wood J, Nelander J, Dufour A, et al. Direct conversion of human fibroblasts to dopaminergic neurons. Proc Natl Acad Sci U S A. 2011; 108: 10343-10348.
16. Karow M, Sanchez R, Schichor C, Masserdotti G, Ortega F, Heinrich C, et al. Reprogramming of pericyte-derived cells of the adult human brain into induced neuronal cells. Cell Stem Cell. 2012; 11: 471-476.
17. Simonsson S, Gurdon J. DNA demethylation is necessary for the epigenetic reprogramming of somatic cell nuclei. Nat Cell Biol. 2004; 6: 984-990.
18. Luna-Zurita L, Bruneau BG. Chromatin modulators as facilitating factors in cellular reprogramming. Curr Opin Genet Dev. 2013; 23: 556-561.
19. Lin TX, Ambasudhan R, Yuan X, Li WL, Hilcove S, Abujarour R, et al. A chemical platform for improved induction of human iPSCs. Nat Meth. 2009; 6: 805-808.
20. Huangfu DW, Maehr R, Guo WJ, Eijkelenboom A, Snitow M, Chen AE, et al. Induction of pluripotent stem cells by defined factors is greatly improved by small-molecule compounds. Nat Biotech. 2008; 26: 795-797.
21. Berninger B, Jessberger S. Engineering of Adult Neurogenesis and Gliogenesis. Cold Spring Harb Perspect Biol. 2016; 8: pii: a018861.
22. Niu W, Zang T, Zou Y, Fang S, Smith DK, Bachoo R, et al. *In vivo* reprogramming of astrocytes to neuroblasts in the adult brain. Nat Cell Biol. 2013; 15: 1164-1175.
23. Guo Z, Zhang L, Wu Z, Chen Y, Wang F, Chen G. *In vivo* direct reprogramming of reactive glial cells into functional neurons after brain injury and in an Alzheimer's disease model. Cell Stem Cell. 2014; 14: 188-202.
24. Weider M, Wegener A, Schmitt C, Kuspert M, Hillgartner S, Bosl MR, et al. Elevated *in vivo* levels of a single transcription factor directly convert satellite glia into oligodendrocyte-like cells. PLoS Genet. 2015; 11: e1005008.
25. Nishiyama A. Polydendrocytes: NG2 cells with many roles in development and repair of the CNS. Neuroscientist. 2007; 13: 62-76.