Novel Tools and Methods

**In Vivo Reprogramming for Brain and Spinal Cord Repair**

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**Abstract**

Cell reprogramming technologies have enabled the generation of various specific cell types including neurons from readily accessible patient cells, such as skin fibroblasts, providing an intriguing novel cell source for autologous cell transplantation. However, cell transplantation faces several difficult hurdles such as cell production and purification, long-term survival, and functional integration after transplantation. Recently, in vivo reprogramming, which makes use of endogenous cells for regeneration purpose, emerged as a new approach to circumvent cell transplantation. There has been evidence for in vivo reprogramming in the mouse pancreas, heart, and brain and spinal cord with various degrees of success. This mini review summarizes the latest developments presented in the first symposium on in vivo reprogramming glial cells into functional neurons in the brain and spinal cord, held at the 2014 annual meeting of the Society for Neuroscience in Washington, DC.

**Key words:** astrocyte; brain repair; in vivo; neuron; NG2 cell; reprogramming

**Significance Statement**

We have had the first symposium on in vivo reprogramming at the 2014 SFN meeting held at Washington DC. Our symposium attracted more than 800 people from around the world. This symposium invited world leaders in this emerging new field to present their most exciting results on in vivo reprogramming glial cells into functional neurons. This minireview discussed the latest developments on in vivo reprogramming and its potential application for brain and spinal cord repair.

Cellular reprogramming has become of great interest in both basic and applied research over the last decade (Graf, 2011). Initiated by the successful nuclear transfer experiments in mammals, the quest arose for a molecular...
The induced pluripotent stem cell technology opened a new avenue using transcription factors to reprogram adult skin fibroblast cells into stem cells, which can be differentiated into a variety of target cells (Takahashi et al., 2007; Yamanaka, 2009). Further studies have demonstrated direct interlineage reprogramming of fibroblast cells into a terminally differentiated cell type, such as neuronal cells, without going through the stem cell stage (Vierbuchen et al., 2010; Pang et al., 2011; Pfisterer et al., 2011). Such direct trans-differentiation technology has been tested not only in cell cultures \textit{in vitro}, but also inside the mouse pancreas, heart, and in particular the brain and spinal cord \textit{in vivo} (Buffo et al., 2008; Zhou et al., 2008; Qian et al., 2012; Grande et al., 2013; Niu et al., 2013; Torper et al., 2013; Guo et al., 2014; Heinrich et al., 2014; Su et al., 2014). At the 2014 annual meeting of the Society for Neuroscience in Washington DC, we had the first symposium on \textit{in vivo} reprogramming and discussed potential applications of reprogramming glial cells into neurons for brain and spinal cord repair. This report summarizes the work in each speaker’s laboratory.

Reprogramming fibroblast cells into induced neurons

Vierbuchen et al. (2010) demonstrated that cells can be directly reprogrammed into even distantly-related cell types. Specifically, they showed that fibroblasts (of mesodermal origin) can be directly converted into functional neurons (which are of ectodermal origin). After a systematic screen of \textasciitilde20 factors, it was found that the combination of the three factors \textit{Ascl1}, \textit{Bm2}, and \textit{Myt1l} was sufficient to convert mouse fibroblasts into cells with neuronal morphology, neuronal marker expression and, most importantly, neuronal function including the ability to generate action potentials and formation of functional synapses. These cells were termed induced neuronal (iN) cells. It was further demonstrated that iN cells can also be formed from human fibroblasts when various combinations of transcription factors were used with or without microRNAs or small molecules (Ambasudhan et al., 2011; Caiazzo et al., 2011; Pang et al., 2011; Pfisterer et al., 2011; Son et al., 2011; Yoo et al., 2011; Ladewig et al., 2012).

These findings sparked great interest in the field and opened several new research avenues. For instance, patient-derived iN cells could be used to investigate pathogenetic mechanisms and reveal cellular phenotypes that could be used as proxy for disease expression and as assay for testing therapeutic interventions such as candidate or novel small molecule drugs (Ming et al., 2011). iN cells or other induced neural cell types that are of more proliferative capacity such as induced neural progenitor cells (iNPCs) or induced oligodendrocyte precursor cells (iOPCs) could also be used as cellular grafts with therapeutic intention, such as for Parkinson’s disease or myelin diseases (Han et al., 2012; Lujan et al., 2012; Thier et al., 2012; Yang et al., 2013). On the other hand, direct reprogramming could be envisioned for \textit{in situ} conversion of non-neuronal cells into neurons. Given the complex manufacturing and regulatory hurdles of living cells as a therapeutic approach, the prospect to accomplish neural regeneration with delivery of small molecules or viruses is very attractive. As discussed in more detail, some initial and promising results have been obtained along these lines.

On a mechanistic level, it is unclear how the expression of a small group of transcription factors can accomplish such a biologically complex task of converting one defined, mature cell type into another. Such cell lineage conversions must include many different cell biological processes like cell polarization, cell-cycle changes, cytoskeletal rearrangements, membrane compartmentalization and proper distribution of ion channels, axonal transport, and synapse formation. Work has begun to map the earliest reprogramming events on the molecular level and found that one of the three main reprogramming factors \textit{Ascl1} has pioneer factor properties, that is it can access closed chromatin in fibroblasts and enables recruitment of other transcription factors and eventual gene transcription (Wapinski et al., 2013). Presumably, a few critical secondarily induced, downstream transcription factors execute different parts of the Ascl1-induced program (Wapinski et al., 2013). Surprisingly, it was also found that the pioneer factor activity of \textit{Ascl1} seems sufficient to induce iN cells without any other reprogramming factors or small molecule addition (Chanda et al., 2014). On the other hand, a closely related factor \textit{Neurog2}, is incapable of converting fibroblasts alone, but very potent to generate iN cells from undifferentiated embryonic stem (ES) cells (Zhang et al., 2013). Current work is investigating the molecular features of \textit{Ascl1} and \textit{Neurog2} that are responsible for these dramatic functional differences.

Cell reprogramming and adult neural stem cells

The concept of neuronal cell reprogramming has broad implications and impact not only in translational neuroscience, but also in basic neurobiology studies. In the adult mammalian brain, neural stem cells (NSCs) persist in a few restricted regions and continuously produce new neurons throughout life. When the in vivo identity of these adult NSCs was first revealed late last century, a surpris-
ing finding was that they share many features with mature astrocytes, one of the most abundant and widely distributed cell types in the adult brain (Doetsch et al., 1999). In fact, recent transcriptome studies have demonstrated a close similarity of the overall gene expression profile between astrocytes and adult NSCs (Beckervordersandforth et al., 2010; Codega et al., 2014). Nevertheless, only NSCs, but not astrocytes, exhibit the capacity of self-renewal and multilineage differentiation, the hallmark of stem cells. Although many regulators of adult NSCs have been identified in the past 2 decades, it is not yet fully understood what the core components of the stemness molecular program are that distinguish NSCs from astrocytes. M.N. and his colleagues used the in vivo reprogramming paradigm to address this long-unresolved issue. They recently demonstrated that the homeodomain transcription factor (TF) Gsx2 and the basic helix-loop-helix (bHLH) transcription factor Ascl1 play vital roles in the activation and neurogenesis in adult NSCs (López-Juárez et al., 2013; Andersen et al., 2014). They tested whether these key regulators of adult NSCs alone can confer any capacities of stem cells to non-stem astrocytes in vivo. Using newly developed transgenic mice in which Gsx2 and Ascl1 can be ectopically expressed in mature astrocytes, they found that these factors induce mature astrocytes to exhibit many features of NSCs, including sustained proliferation and neurogenesis in vivo and generation of self-renewing neospheres in vitro. They further presented evidence that paracrine and autocrine signaling through transforming growth factor β receptors plays a role in regulating neurogenesis by Gsx2- and Ascl1-reprogrammed astrocytes. It will be interesting to investigate whether other reprogramming factors exhibit a similar capacity to convert astrocytes and other cell types into NSCs. As such, neuronal cell reprogramming has opened a new avenue of research on the mechanisms of cell type specification in the nervous system.

In vivo reprogramming adult astrocytes to neural progenitors

Although neurons are frequently lost in response to injury or degeneration, astrocytes on the other hand become reactive, proliferative, and form glial scars. Reactive gliosis and glial scars are initially protective in restricting further spreading of damages but are in long-term deleterious by acting as both physical and biochemical barriers to neural regeneration (Sofroniew, 2009).

C.-L.Z. and colleagues developed a strategy to convert resident astrocytes to proliferative neural progenitors and functionally mature neurons in the adult brain and spinal cord (Niu et al., 2013, 2015; Su et al., 2014). After screening a dozen of transcriptional regulators that play critical roles in the regulation of neural stem cells, neurogenesis and cell reprogramming, Niu et al., 2013 identified that the stem cell factor SOX2 alone is sufficient to robustly induce DCX+ neuroblasts in the adult mouse brain. Encouragingly, SOX2 has been found to possess powerful reprogramming activity (Karow et al., 2012; Ring et al., 2012). Genetic lineage mappings confirmed that these induced adult neuroblasts (iANBs) indeed originate from resident astrocytes. A time course analysis showed that iANBs are progressively generated and can be identified even in the aged mouse brain. Interestingly, BrdU-incorporation and Ki67-staining, which are indicators of cell proliferation, showed that a fraction of iANBs are still dividing, a feature consistent with native neuroblasts. Resembling the cellular sequence of endogenous neurogenesis from neural stem cells, genetic lineage tracings and immunohistochemistry further demonstrate that SOX2-dependent in vivo reprogramming of astrocytes passes through a neural progenitor stage prior to the appearance of iANBs (Niu et al., 2015). Together, these data suggest that SOX2-driven cell fate conversion is a nonlinear process with the potential of one reprogrammed astrocytes giving rise to multiple iANBs.

Additional factors are required for iANBs to become functionally mature neurons in the adult brain. Niu et al. (2013, 2015) identified that the neurotrophic factors BDNF and noggin are sufficient to promote survival and maturation of the newly reprogrammed neurons. Moreover, the small molecule valproic acid (VPA), a clinically used drug for the treatment of epilepsy, mania, and migraine, can replace those neurotrophic factors. Electrophysiology using live brain slices from genetically traced mice showed that astrocyte-converted neurons are electrically mature and make appropriate connections within the local neuronal networks. By applying the same reprogramming strategy, Su et al. (2014) demonstrated that SOX2 can similarly convert resident astrocytes into mature neurons in the adult spinal cord post-traumatic injury. These induced neurons can make synaptic connections with local motor neurons (Su et al., 2014).

In summary, SOX2 overexpression initiates a stepwise reprogramming process that converts resident astrocytes to expandable neural progenitors, which eventually generate mature neurons in the injured adult central nervous system. This SOX2-driven, multistep reprogramming process may provide the much-needed neurons for neural regeneration after injury or degeneration.

In vivo reprogramming NG2 glia into neurons

B.B. reported recent work aiming at reprogramming resident glia into neurons in the context of a highly invasive cortical injury in vivo. Work from his team had previously demonstrated that astrocytes can be reprogrammed into fully functional neurons in vitro by retrovirus-mediated expression of Ascl1 or Neurog2 (Berninger et al., 2007; Heinrich et al., 2010). Moreover, combined expression of Sox2 and Ascl1 had been found to convert pericytes isolated from the adult human brain into induced neurons (Karow et al., 2012), encouraging his team to study now the same combination of transcription factors in vivo (Heinrich et al., 2014). When the cerebral cortex of adult mice was subjected to a local injury caused by a stab wound, resident macroglia and microglia were found to respond with increased proliferation as described previously (Buffo et al., 2005; Simon et al., 2011). Three days after injury, these proliferating glial populations then could be targeted by retroviruses en-
of glia into neurons in vitro and in vivo using viral mediated gene delivery. Once formed, the new neurons acquire mature neuronal characteristics in a stepwise fashion, and at the same time down-regulate glia-specific genes. M.P.’s group, and others, have shown that both resident astrocytes and NG2 glia can efficiently be converted into neurons that mature, function and integrate into existing neural circuitry (Niu et al., 2013, 2015; Torper et al., 2013, 2015; Guo et al., 2014; Heinrich et al., 2014; Su et al., 2014; Liu et al., 2015). However, unlike for direct neural conversion in vitro, it is yet not possible to direct the formation of dopaminergic neurons via direct conversion in vivo. In vitro, it is possible to change the transcription factor combination used for direct neural conversion of fibroblasts and astrocytes in order to generate subtype-specific neurons. For example, Ascl1 (Mash1), Brn2a, and Myt11 (ABM) yield glutamatergic neurons (Vierbuchen et al., 2010), whereas Ascl1 (Mash1), Lmx1a/b, and Nurr1 (ALN) results in the formation of dopaminergic neurons when converting fibroblasts and astrocytes in vitro (Caiazzo et al., 2011; Torper et al., 2013). In our studies in vivo, however, the ALN combination fails to convert resident astrocytes or NG2 glia into dopamine neurons in vivo, which has been published recently (Torper et al., 2015).

Thus, to harness the full potential of in vivo conversion for brain repair, one has to learn how to generate specific regionalized neuronal cell types of need in a particular disease, for example, dopamine neurons for Parkinson’s disease. It is also important to keep in mind that all diseases affecting the brain may not be suitable targets for brain repair via in vivo reprogramming due to loss of multiple cell types, diverse loss of neurons scattered in various brain regions, etc. Nevertheless, the ability to create new neurons from resident glia in the brain opens up for new, and previously unconsidered, possibilities for brain repair.

**Therapeutic potential of in vivo reprogramming**

G.C. and colleagues have been focusing on the potential applications of in vivo reprogramming for brain repair. They have first used a brain-stab injury model to test whether injury-induced reactive astrocytes can be directly reprogrammed into functional neurons in the adult mouse cortex. When ectopically expressing a single bHLH neural transcription factor NeuroD1 in reactive astrocytes at the stab injury sites, they were able to reprogram reactive astrocytes directly into functional neurons (Guo et al., 2014). This was achieved with retroviruses that only express NeuroD1 specifically in dividing reactive glial cells in the adult mouse cortex, where normal astrocytes do not divide under physiological condition. Patch-clamp recordings in cortical slices demonstrated that these NeuroD1-converted new neurons are functional, as shown by repetitive action potentials and robust synaptic events, suggesting that the newly converted neurons form functional synapses with other neurons and have successfully integrated into local circuits. Importantly, these astrocyte-converted new neurons could survive 2–8 months in the adult mouse cortex, indicating their thera-
peutic potential for brain repair. Besides this brain injury model, Chen’s group further tested in vivo reprogramming in a mouse model of Alzheimer’s disease (AD). They show that the 5xFAD mouse brain has numerous reactive astrocytes in the cortex, and injection of NeuroD1 retrovirus into the 14-month-old AD mouse brain can still generate many functional neurons (Guo et al., 2014), suggesting that such glia-neuron conversion technology may indeed be potentially applicable for human brain repair. Importantly, NeuroD1 directly converts astrocytes and NG2 cells into neurons, without inducing a transient progenitor stage, and the conversion efficiency can be as high as 90%, making it a potential candidate for therapeutic treatment.

G.C. further discussed unpublished work at the symposium, including direct conversion of NG2 glia into GABAergic neurons and chemical reprogramming of human astrocytes into functional neurons using a cocktail of small molecules.

Concluding remarks

Although the vast majority of cell reprogramming studies are still conducted in cultured cells, in vivo reprogramming starts to attract attention of both stem cell biologists and translational researchers aiming for clinical applications. Compared to conventional stem cell therapies involving the in vitro manufacturing and transplantation of cultured cells, the approach to reprogram specific cell types in vivo greatly reduces the risks associated with conventional cell therapy. Already, animal studies have indicated promising potential for the in vivo reprogramming approach to regenerate functional neurons in injured or diseased brain and spinal cord. Several new articles have recently been published on in vivo reprogramming or related studies over the past several months since our first symposium held at the 2014 SFN meeting (Liu et al., 2015; Masserdotti et al., 2015; Niu et al., 2015; Raposo et al., 2015; Torper et al., 2015). Of course, this is still the proof-of-concept that in vivo reprogramming may be useful for brain and spinal cord repair and there are many challenges ahead. For example, it has been successful to reprogram glial cells into glutamatergic and GABAergic neurons inside the mouse brain, but reprogramming dopaminergic neurons from glial cells in vivo has been difficult so far. Furthermore, it will be important to assess the long-term functional effects of neural circuits after in vivo reprogramming. It is also necessary to investigate whether the gene delivery and reprogramming procedure is safe in vivo in a variety of animal models including nonhuman primates, before applying such in vivo reprogramming technology in clinical trials. Despite significant challenges, we hope that concerted efforts of a growing research community will tackle these problems and some day may realize these exciting therapeutic possibilities.

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