stem cell research&therapy

COMMENTARY

Conversion of pericytes to neurons: a new guest at the reprogramming convention

Emmanuel Nivet[1], Ignacio Sancho-Martinez[1] and Juan Carlos Izpisua Belmonte*[1,2]

Abstract

Reprogramming strategies allow for the generation of virtually any cell type of the human body, which could be useful for cell-based therapy. Among the different reprogramming technologies available, direct lineage conversion offers the possibility to change the phenotype of a cell type to another one without pushing cells backwards to a plastic/proliferative stage. This approach has raised the possibility to apply a similar process *in vivo* in order to compensate for functional cell loss. Historically, the cerebral tissue is a prime choice for developing cell-based treatments. As local pericyte accumulation is observed after central nervous system injury, it can be reasoned that this cell type might be a good candidate for the conversion into new neurons *in vivo*. In this article, and by focusing on recent observations from Karow and colleagues demonstrating the possibility to convert human brain-derived pericytes into functional neurons, we present a brief overview of the state of the art and attempt to offer perspective as to how these interesting laboratory findings could be translated in the clinic.

Reprogramming strategies are highly promising for the development of future regenerative medicine approaches. Over the past 60 years, from the first nuclear transfer experiment to the description of cell fate conversions by forced expression/inhibition of cell-type specific transcription factors (TFs) and/or miRNAs, a great deal of evidence showing cell identity switches has been accumulated [1]. Numerous cocktails of TFs have to date been identified for the conversion of somatic cells all the way back to pluripotency or into more specialized cell types. Accordingly, the emergence of cell fate conversion strategies represents a new unexpected source for generating any desired cell type that could be of interest for the clinic. These lineage conversion strategies could be divided into: direct conversion approaches, in which tissue-specific TFs are employed and characterized by the lack of proliferation and/or progenitor generation; and indirect conversion approaches, based on the use of so-called pluripotency factors. Indirect lineage conversion, as opposed to direct conversion, is driven by a partial dedifferentiation step, with potential for the generation of expandable progenitor populations, followed by redifferentiation into specific populations (for a recent review see [1]).

Noticeably, cerebral tissue has always been one of the most studied tissues for the development of cell-based therapies, sustained by the hope that cell transplantations could facilitate the replacement of lost neural tissue and/or protect from neurodegenerative processes. Although several cell types have demonstrated encouraging results in animal models, neural stem cells and their derivatives are naturally seen as the most suitable cellular products. Taking into account that access to such cellular material is technically and ethically difficult, the advent of lineage conversion strategies has opened new vistas towards the generation of neural cells as well as towards the exploration of new treatment avenues.

In 2010 the Wernig laboratory was the first to meet this challenge by defining a set of three TFs – that is, Ascl1, Brn2 and Myt1l – allowing for the generation of functional neurons upon overexpression in mouse fibroblasts [2]. Later on, the same group demonstrated that addition of NeuroD1 to this cocktail was sufficient to achieve the same conversion in human fibroblasts [3]. Numerous reports have since then reproduced and extended this discovery by identifying other lineage specifiers able to convert fibroblasts into neural progenitors or more specialized neurons such as motoneurons [4] and dopaminergic neurons [5]. Alternatively, by combining pluripotency-associated reprogramming factors with neural specifiers or defined media, other laboratories have reported that it is feasible to convert fibroblasts into expandable neural stem cells [6].

From these and other reports, two main lineage conversion strategies can be envisaged for clinical

*Correspondence: belmonte@salk.edu or izpisua@cmrb.eu
[1]Gene Expression Laboratory, Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA
Full list of author information is available at the end of the article

applications: the generation of the desired cell type(s) *in vitro* and its further transplantation; and the local *in vivo* conversion of one cell type into the one(s) required, in a similar way to what has been experimentally done with pancreatic cells. As a common denominator for most of these studies, however, fibroblasts represent the starting cell type of choice for achieving this lineage conversion; cord blood cells [7] and astrocytes [8] are exceptions to this rule. The latest strategy might thus not be the most appropriate unless other cell types present in the brain, and not as essential for brain functions as neural cells, could be reprogrammed.

Interestingly, a recent report from the Berninger laboratory convincingly extended the spectrum of somatic cell types able to give rise to neurons upon forced expression of TFs [9]. In their report, Karow and colleagues describe the *in vitro* conversion of pericytes, residing in the adult human brain, using only two TFs: Sox2 and Mash1 (Ascl1). The authors showed that the so-called human pericyte-derived induced neurons acquired molecular marks and electrophysiological properties resembling those of primary mature neurons, with further maturation when co-cultured with murine neurons. Even though the final evidence for the phenotypic identity of the newly generated neurons is not yet provided, they seem to display the hallmarks of GABAergic interneurons. Of note, the authors observed a conversion rate of about 20% but also an important cell death (≈30%) in the co-transfected cells. Although the mechanism of action controlling this lineage conversion is not fully identified, Sox2 being a pluripotent factor as well as a neural lineage specifier, a synergic effect may occur consisting of Sox2-induced partial dedifferentiation alongside activating a neuronal program with both Sox2 and Mash1. Of importance, the authors showed that converted cells do not undergo cell division during this process, supporting the idea that this occurs via a direct conversion mechanism.

In conclusion, pericytes not only represent a new cell type suitable for neuronal conversion but also provide a new cell candidate for *in vivo* approaches. Indeed, similarly to astrocytes, pericytes have been identified as one of the core components of post-injury scarification in the central nervous system [10]. Considering that pericytes are amenable to being converted into neurons, we can imagine that these cells, localized within or close to an injured area, may be a good target for *in vivo* conversion without much effect on the surrounding neural cells. However, it will be important to specifically convert pericytes *in vivo* but also to limit the cell death associated with this process. The role of resident pericytes after injury should also be precisely studied to avoid any side effect upon conversion. Importantly, both central nervous system injuries and neurodegenerative processes generally affect more than one cell type, implying that several specialized cells counteracting the effects observed in the diseased brain might be needed.

All in all, the study by Karow and colleagues presents pericytes as a new contender in the race to the operating room but we have a long way to go before a particular cell type gets elected.

Abbreviations
miRNA, microRNA; TF, transcription factor.

Competing interests
The authors declare that they have no competing interests.

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Author details
[1]Gene Expression Laboratory, Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA. [2]Center for Regenerative Medicine in Barcelona, Dr. Aiguader 88, 08003 Barcelona, Spain.

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