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Short Commentary

Transdifferentiation in Neuroscience: Lights and Shadows

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Adult cells are believed to maintain their differentiated status under stable homeostatic conditions, while cellular identity can become plastic when homeostasis is perturbed such as during an injury and inflammation [1]. Indeed, it is now evident that cell identity is more flexible and plastic than previously thought. In particular, recent studies have shown that it is possible to influence cell fate through artificial manipulation such as exogenous expression of a set of Transcription Factors (TFs) that results in the reprogramming of adult skin fibroblasts to a pluripotent state [2]. In addition, recent reports have demonstrated that one type of differentiated somatic cell can be directly reprogrammed to another type of cell, without rejuvenation to a pluripotent state, in a process called transdifferentiation [3,4]. Transdifferentiation is an epigenetic acquisition by a cell of a given type of the properties and features of another cell type, loosing its own phenotype [5].

Adult brain has very limited regeneration capability, thus, the possibility of a direct neuronal reprogramming from non-neuronal cells, by passing a pluripotent state,would induce the formation of precious neuronal cells. This direct cellular generation thus represents a potential remedy for neuronal loss caused by brain injuries or neurodegeneration. In addition, the direct conversion of patient-specific cells could be used to implement disease-relevant *in vitro* platforms to generate models for neurodegenerative diseases, identify targets, and screen potential therapeutic drugs. Indeed, hundreds of millions of people worldwide are affected by neurological disorders, making them one of the greatest threats to public health.

This Commentary discusses current knowledge on direct reprogramming towards neuronal cell identity, and more specifically, recent advances in trasdifferentiation mediated by the exclusive use of chemical cocktails, remarking advantages and limits. To our opinion, direct reprogramming approaches represent an innovative strategy to overcome major barrier of the in accessibility of human brain to obtain human neurons for studies of pathological mechanisms of diseases. Moreover, directly converted induced neurons (iNCs) from human donor-derived fibroblasts possess important features of cellular aging, including global transcriptomic changes, nuclear pore defects, and DNA methylation, rendering them a valuable tool for the study of age-related neurological diseases [3,6-8].

Among the various strategies to obtain direct reprogramming, ectopic expression of TFs in non-neuronal cells has generated neurons and neural progenitors both *in vitro* and *in vivo* [9-17]. Direct conversion by TFs stands on their ability to bind to in accessible neuronal genes in differentiated non-neuronal cell types which are generally called as pioneer TFs.

The first direct conversion strategy was achieved by the over expression of the three TFs, namely Ascl1, Brn2, and Myt1l (BAM factors), in mouse fibroblasts [18], and was the nextended to BAM with NeuroD1 to convert human fibroblasts to iNs with a simila refficacy [19]. Recently, it has been suggested that a huge variety of TF combinations can be applied to generate subtype-specific iNs from fibroblasts and TF screening studies for iNs conversion have led to the identification of additional pro-neuronal factors, suchas Brn3a/b/c, Brn4s, and Ezh2 [20,21].

More interestingly, TFs and endogenous genes vital to the transdifferentiation process can be specifically targeted and silenced or upregulated, using methods that focus on the direct manipulation of DNA or the epigenetic environment, such as CRISPR/Cas9 [22,23].

Moreover, the ability to drive direct reprogramming is not limited to TFs, as non-coding RNAs can promote it as well. In addition, the culture conditions, including increased time in culture and developing coculture with astrocytes, may have an impact in terms of both phenotypic fate and efficiency of reprogramming.

The use of viral vectors to introduce exogenous transgenes into cells is currently the most prominent method to induce transdifferentiation. Generally, lentiviruses and retroviruses are mostly used due to their ability to effectively integrate directly into the genome of the host cell and confer a proper level of TF expression. However, viral delivery of TFs possesses undesirable side effects, including possible mutations leading to oncogenesis, thus posing problems for possible clinical trial application. That is the reason why non-integrating vectors have been developed, although associated with lower efficiencies of transdifferentiation, including: Sendai virus, plasmid vectors, minicircles, and mRNA vectors which remain in the cytoplasm where they are translated into proteins. Alternative non-viral methods, such as transient transfection and electroporation, can be also applied, however, due to their low efficiency, transgene silencing, inflammation and poor nuclear uptake, are less commonly used in transdifferentiation studies [24]. Lately, the use of Protein Transduction Domains (PTDs)

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fused to TFs allows the direct delivery of exogenous TFs avoiding the problems associated with DNA integration into the hostgenome [25].

Besides TFs, small molecules, modulating specific targets and epigenetic mechanisms, have been used to produce neural progenitors [26] and neurons [27-29] in *in vitro* cultures.

Small molecules can be applied in combination with viral agent-mediated TF delivery to improve the reprogramming efficiency [30-35] although, chemical reprogramming alone can be easily administrated and converted into therapeutic intervention. In the last years, several groups have identified combinations of small molecules capable of transdifferentiating somatic cells such as fibroblasts, astrocytes and even glioblastoma cells into neurons [26-29,32,36].

Small molecules can convert human astrocytes or fibroblasts into functional neurons, with a yield of up to 85% neurons from fetal and adult astrocytes [28,29], which is lower from human fibroblasts, with an efficiency of no more than 15% [27]. For sure, fibroblasts are better starting cells for direct neuronal reprogramming because of easier access for acquisition than astrocytes, although their lower reprogramming efficiency to neurons needs to be increased for broader application in neurological diseases. For example, Yang et al., [37] reported that human fibroblasts can be efficiently and directly reprogrammed into glutamatergic neurons by serially exposing cells to a combination of twelve small molecules. The sec iNs displayed neuronal transcriptional networks, and also exhibited mature firing patterns and formed functional synapses.

Although many reports have demonstrate dthat small molecules can convert one type of terminally differentiated somatic cell to another fully differentiated cell type, there are still various major aspects ahead that must be overcome. Indeed, protocols using small molecules produce mainly glutamatergic subtypes with rare gabaergic and dopaminergic neurons. The inability to produce the neuronal subtypes which are lost in neurodegenerative disorders like Parkinson's Disease, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Huntingdon's Disease represents a major limitation in current small molecules transdifferentiation field. However, it was showed that a single TF such as ASCL1, using a novel protein intracellular delivery technology, in combination with the small molecules LDN193189, SB431542, DAPT and valproic acid can rapidly reprogram astrocytes into mature GABAergic and glutamatergic interneurons with high efficiency [25]. Moreover, Chabrat et al., developed a novel *in vitro* model of dopaminergic-like neurons derived from human nasal olfactory stem cells through a six step transdifferentiation protocol based on a specific combination of signaling pathway modulators [38].

Thus, it is reasonable to envisage that slight modifications of the chemical recipe may yield additional neuronal lineages optimizing and harnessing the small molecule-mediated reprogramming approach, leading to remarkable advances in disease modeling and possibly regenerative medicine in the future.

The main disadvantages of transdifferentiation by chemical approach to generate brain cells with specific properties consist in a low efficiency, a mixed population of neurons with different degrees of maturity and a unique subtype of neurons, although capable to maintain the age-related fetaures associated with the human pathology. Forced expression of exogenous TFs for the direct reprogramming is supposed to damage proper epigenetic marks and genome integrity, where as chemical compound-based conversion should be milder, leading to a better conservation of the ageing conditions. Thus, we believe that the chemical strategy may represent a new valid method for generating cells for both basic research and clinical applications. It is important to consider that the rapid metabolic transition that takes place during the fate switch from somatic cell to neuron puts enormous stress on the cell, leading to the formation of Reactive Oxygen Species (ROS), known to induce toxicity and affect cell fate regulation, representing a major barrier to transdifferentiation [39]. For this reason an intermediate stage of reprogramming would reduce this oxidative stress, promoting a safer transition between cell fates and improving efficiency [16]. In this respect, the generation of neural stem or progenitor cells (NPCs) from other somatic cells, can largely improve the efficiency of the protocol since each neural stem cell can produce several neurons.

Small molecules can also facilitate the approach of Cell Activation and Signaling-Directed (CASD) reprogramming, which leads cells into an epigenetically activated transition state (cellactivation) that, in conjunction with lineage-specific signals (signaling-directed), reprograms somatic cells into NPCs [40-44]. In this respect, Zhu et al., demonstrated that a single gene, Oct4, in conjunction with a chemical cocktail containing CHIR99021, A-83-01, NaB, LPA, rolipram, and SP600125 was sufficient to convert human fibroblasts into expandable NPCs [45].

The most exciting perspective of direct reprogramming is the possibility that it might be achievable in patients *in vivo*. Performing *in vivo* transdifferentiation would eliminate the need for cell transplantation and immunosuppression depending on the target application. However, potential adverse effects of direct reprogramming *in vivo* could include in appropriate differentiation into other cell types or even tumor cells. In addition, induced cells could be dysfunctional and detrimental to the brain structure.

In animal models, transdifferentiation *in vivo* is now currently feasible, revealing the importan trole of resident glial cells in the generation of specfic neurons to restore lost neuronal circuitries. For example, reactive astrocytes and NG2 cells can be directly reprogrammed into functional neurons inside mouse brains with the expression of a single neural TF, NEUROD1 [14]. Other TFs, such as neurogenin 2 (NGN2), ASCL1, and SOX2, have also been reported to reprogram glial cells into neurons both *in vitro* and *in vivo* [46].

Unfortunately, so far, studies have failed to induce chemical transdifferentiation *in vivo* accomplished only with small molecules resulting efficient just in promoting an increase in adult brain neurogenesis [47].

In conclusion, over the past years, several strategies for direct cellular reprogramming have been developed to generate brain cells with age-preserved features rendering them a valuable tool for many applications such as aged brain modeling and age-related diseases.

Although direct transdifferentiation methods, due to the low efficiency, are quit elimited, there is ongoing research that aims at improving this limit specially with the advent of *in situ* transdifferentiation, and with the emergence of CRISPR/Cas9 system as an alternative to TF overexpression methods. In addition, although some disadvantages need to be overcome, transdifferentiation by chemical reprogramming remains an important tool not only *in vitro* for disease modeling, new biomarkers discovery and drug screening, but also for possible application in regenerative medicine.

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