Dopaminergic control of autophagic-lysosomal function implicates Lmx1b in Parkinson's Disease, Nat Neuroscience

Reviewer: Lucy Collins PhD Student at the John Van Geest Centre for Brain Repair Cambridge.

Reprogramming of somatic cells to alternative lineages is an attractive strategy for modeling inaccessible cells in pathological conditions such as diabetes mellitus, myocardial infarction and in neurodegenerative conditions like Parkinson's Disease. Induced neuron (iN) technology offers an experimental method to potentially enable the manipulation of disease relevant cells. Dermal fibroblasts isolated from a skin biopsy can be directly converted into neurons using defined transgenes introduced into the cell through viruses. This technique is new in the field and many groups are striving to optimise many aspects of this conversion process.

A recent paper aiming at deriving iN cells from Zhao et al, reported that the factor Neurogenin 2 (Ngn2) enhances the production of iN's. This factor was previously reported by Liu and colleagues, also to be an important pro neuronal factor for converting adult fibroblasts (Liu et al., 2013). Many combinations of transgenes have been tried but the best combination for adult fibroblast conversion has yet to be decided on. Marius Wernig and colleagues defined the set criteria for iN cells and acknowledged that various degrees of reprogramming can be achieved in the dish but complete reprograming should produce a cell with a distinct morphology that expresses neuronal genes and fires action potential with evidence of synaptic transmission (Yang, Ng, Pang, Südhof, & Wernig, 2011).

In this current paper by Zhoa et al, the starting population of fibroblast are devoid of any neuronal markers, and after conversion levels of Tuj and MAP2 in these reprogrammed cells were detected as well as more specific neuronal markers such as GABA and vGlut. These converted cells also fired action potentials and had neurotransmitter receptors present.

The limitations of this work and indeed all iN work is that the efficiency of conversion of adult iN cells is still very low. The iN end product remains a heterogenous population of starting dermal fibroblast with iN cells at various degrees of reprogramming. Until such times as this is resolved the value of these cells will remain limited.

Liu M-L, Zang T, Zou Y, Chang JC, Gibson JR, Huber KM, & Zhang C-L. *Small molecules enable neurogenin 2 to efficiently convert human fibroblasts into cholinergic neurons.* Nature Communications, 2013:4;2183. doi:10.1038/ncomms3183

Yang N, Ng YH, Pang ZP, Südhof TC, & Wernig M. *Induced neuronal cells: how to make and define a neuron.* Cell Stem Cell, 2011;9(6):517-25. doi:10.1016/j.stem.2011.11.015

Zhao P, Zhu T, Lu X, Zhu J, & Li L. *Neurogenin 2 enhances the generation of patient-specific induced neuronal cells.* Brain Research 2015. doi:10.1016/j.brainres.2015.04.027

Neurogenin 2 enhances the generation of patient-specific induced neuronal cells

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An improved understanding behind the selective loss of dopaminergic (DA) cells in Parkinson's disease needs to be understood in order to develop better therapies. A recent publication in Nature Neuroscience investigates what is particularly sensitive about DA cells and what factors maintain their cellular function over a lifespan. LIM homeobox transcription factor (Lmx1a and Lmx1b) proteins are known to be developmental drivers of DA neurons. Genetic variations in these proteins have also been flagged up in genome wide association studies as being implicated in PD, and in recent stem cell modeling studies such as induced pluripotent stem cells (iPS) and induced neurons (iN) conversions show that the Lmx1 transgenes are important transcription factors for DA specification.

The function of Lmx1b in adult DA neurons is unclear, to investigate this Laguna et al, use Cre recombinase under the dopamine transporter (DAT), to selectively deplete the Lmx1 proteins in adult mouse DA neurons. Laguna and colleagues found that loss of Lmx1b resulted in dysfunction of the dopaminergic synapse, inclusions of electron-dense protein aggregates in neuronal terminals and degeneration of DA neurons mimicking early cellular degeneration in PD. The transgenic animals also reflected some of the common motor impairments and also early anosmia associated with PD (Laguna et al., 2015).

The authors also found loss of Lmx1b expression also resulted in downregulation of key proteins involved in the lysosome autophagosome pathway (ALP) including LC3I-II, Lamp1 and 2, beclin, p62 cathepsin D and TFEB. The lysosomal pathway has been implicated in PD from genetic and environmental observations. The commonest single genetic risk factor for the development of PD are mutations in the lysosomal enzyme glucocerebrosidase GBA, which when homozygous or compound heterozygous cause Gaucher's disease.

Therefore this paper highlights a dual role of Lmx1b, namely it is important in the maintenance of DA neurons and their functioning ALP and as such agents that can affect its expression maybe of benefit in more than one way in PD patients.

Laguna A, Schintu N, Nobre A, Alvarsson A, Volakakis N, Jacobsen JK, et al. *Dopaminergic control of autophagic-lysosomal function implicates Lmx1b in Parkinson's disease.* Nature Neuroscience, 2015;18(6):826-35. doi:10.1038/nn.4004

Hold on Hope?

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Is optimism a good thing? In most situations the ability to see a hopeful outcome from a difficult set of circumstances is probably helpful allowing an individual to persevere in spite of the daunting challenges they face. What about optimism which is pegged onto the most unlikely of outcomes?

These are the themes that stalk many conversations with family members of those who are recovering from brain injury. The reactions and coping mechanisms are often different between groups of people, but how should we approach the fine line between expectation and optimism? The dichotomy of encouraging optimism versus fostering realism is something that fills discussion with family members in the context of brain injury. There are a number of different viewpoints on how to manage this difficulty within the psychological literature but little in the way of defined evidence.

This paper explores familial optimism in the post-acute stage of acquired brain injury from the inpatient setting and onto discharge. By comparing questionnaires assessing a number of different domains around emotional wellbeing and perceived control administered longitudinally over the course of 18 months, 5 hypotheses were evaluated;

1) Family members are unrealistically optimistic in the post-acute phase.
2) There is a negative emotional impact when optimistic expectations are not fulfilled.
3) Discharge triggers a downward adjust-

ment of expectations and consequent emotional crisis.

4) Optimism about consequences and controllability will lead to better emotional wellbeing and less anxiety and depression.
5) Optimism about controllability will result in greater engagement in the rehabilitation process.

Unfortunately (and, perhaps, predictably) family members were usually over-optimistic in their estimations of how effective treatment and rehabilitation were likely to be while underestimating the impact that the brain injury would have on the family as a whole. Where family members' expectations were not fulfilled there was a negative emotional impact (with a correlation between decline in emotional wellbeing and large variances in expectation and outcome). In spite of this, discharge home was not found to precipitate emotional crises in family members. In the initial stages following the brain injury, optimism is associated with greater emotional wellbeing and it would seem that the negative impact of unrealistic optimism is only manifest later on in the post-acute period. Familial optimism is associated with a greater engagement in the rehabilitation process, which is obviously of great importance particularly where family members are going to adopt a caring role on an ongoing basis.

Although perhaps none of these results on their own are particularly surprising and there may be little that can done to affect an individual's perspective and expectations following brain injury, taken as a whole they serve as a valuable reminder of the importance of consistent, clear and realistic communication with families from the earliest stage. A poorly considered prognostic discussion on the neuro ITU may have profound and long-lasting effects on a family's perceptions and hopes. The preservation of the emotional wellbeing of family members is important both in keeping them involved with the rehabilitation process and for their own health.

Riley GA, Hough A, Meader LM, Brennan AJ. *The course and impact of family optimism in the post-acute period after acquired brain injury.* BRAIN INJURY 2015;14:1-9.