GABA signalling: a route to new pancreatic β cells in type 1 diabetes?

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Stand first

An ability to convert between pancreatic islet cell types may provide a new approach to replace insulin-secreting β cells destroyed by autoimmune attack in Type 1 diabetes. Two papers, which have recently appeared in Cell [1; 2], describe how this might be achieved.

Diabetes mellitus (DM) affects >400 m individuals worldwide and new treatments are desperately needed to treat this growing epidemic. Pancreatic β cells, located within the islet micro-organ, are the sole source of secreted insulin in mammals [3]. Autoimmunity-induced destruction of β cells is the underlying cause of Type 1 DM, whereas more subtle decreases in cell mass and functional impairment drive Type 2 DM [3]. Strategies to replace destroyed β cells in T1 DM are currently hindered by the absence of sufficient transplantable material, usually obtained post-mortem from donors. New approaches, conceivably involving the regeneration of β cells in vivo, are therefore urgently sought.

Pancreatic β cells are co-located within the islet alongside other hormone-secreting cells, including glucagon-secreting α cells, somatostatin-secreting δ cells and others. Although enhanced β cell proliferation has been considered a possible approach to treating T1 DM, the near complete loss of β cells in this disease means that neogenesis from an alternate cellular pool may be more realistic, especially given mounting evidence for islet cell plasticity.
Towards this end, earlier studies by Herrera and coworkers [5], and Collombat and colleagues [6], demonstrated the possibility of converting α to β cells *in vivo*. This occurred in response to the destruction of β cells, or after modifying the expression of critical transcription factors, respectively. However, a means of achieving such a fate switch in a controlled and therapeutically tractable manner has so far proved elusive.

Firstly, Li et al. established an assay for Arx function, a transcription factor required to maintain α cell phenotype. Over-expression of this factor in the clonal β cell line MIN6 provided the basis of a screen for small molecules which inhibited Arx, consequently increasing insulin gene expression. In this way, the authors identified artemins, including the antimalarial drug artemether, as effective regulators of Arx function and cell identity. A further chemical proteomics screen then identified gephyrin as the likely receptor for artemether. Gephyrin is a key regulator of γ-aminobutyric acid (GABA) synthesis and GABA_A receptor trafficking. Strikingly, artemether increased β cell numbers *in vivo* in both mice and zebrafish, and lineage tracing analysis showed this was due to α to β cell conversion [1]. Artemether-treated clonal α cells (αTC1-6) also displayed Arx exclusion from the nucleus and altered depolarisation-induced Ca^{2+} dynamics [1], consistent with enhanced GABA_A receptor expression. Importantly, single cell RNAseq experiments demonstrated similar effects in human α cells.

Complementing the above study, Ben-Othman and co-workers [2] performed a transcriptional screen to identify genes up-regulated by overexpression of *Pax4* in α cells, a manoeuvre which favours α to β cell switching [6]. Many of the most strongly up-regulated genes were involved in GABA signalling. Correspondingly, treatment of αTC1-6 cells with GABA decreased the expression of Arx, suggesting that the neurotransmitter favours the conversion of α to β cells *in vivo*. Providing a direct demonstration of this hypothesis, treatment of mice for 2 or 6 months led to a remarkable (>3-fold) increase in β cell mass. Again, lineage tracing using a glucagon promoter-driven Cre to drive β-gal expression
revealed that the vast majority of the “additional” β cells were derived from a glucagon-positive progenitor.

Extending this work to a model of T1DM, these authors [2] went on to show that the effects of β cell destruction with the chemical agent streptozotocin were reversed by GABA and that this resulted from the generation of β from α cells.

There are, nonetheless, several intriguing aspects of these studies which will require further investigations. Firstly, within the intact healthy islet, GABA is chiefly released from β cells and, at least in the case of rodent islets where blood flow is known to be in the direction β to α cells [7], is likely then to act on α cells. According to the new findings, GABA action should consequently favour conversion of α to β cells. The loss of this input therefore seems unlikely to explain α to β cell conversion after the artificial destruction of β cells in mice [5] and would be expected to hinder β cell neogenesis after this destruction of these cells in T1 DM.

Secondly, what signalling mechanisms within α cells are responsible for the observed changes in Arx expression, and ultimately the switch to an β cell phenotype? Whilst increased Ca\(^{2+}\) can elicits dramatic changes in cellular phenotype, for example after oocyte fertilisation [8], how a decrease in Ca\(^{2+}\), as provoked by artemether or GABA\(\alpha\) receptor activation (prompting an influx of Cl\(^{-}\) ions) [1], could alter gene expression in the α cell in such a dramatic manner remains to be established. Identification of the molecular machinery linking GABA-induced changes in Ca\(^{2+}\) to altered Arx localisation and expression represent an important new challenge.

What is the immediate translational potential of these results? GABA\(\alpha\) receptor agonists are in current clinical use as a treatment for epilepsy [9] whilst artemether is widely deployed as an antimalarial drug [10]. Both are therefore considered safe for use in humans. Clinical
trials with these agents should therefore be feasible and should reveal whether GABA treatment might provide the basis of exciting new regenerative treatments for T1 DM (Fig. 1).

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Figure 1. Mechanisms through which GABA receptor agonists or artemesins may be used to provoke an α to β cell fate switch to correct the destruction of β cells in T1 DM. Clockwise from top left: β cells (green) are destroyed in T1 DM, leaving α cells (red) largely unaffected. Artemesins prompt the up-regulation of GABA_A receptors (orange), favouring the actions of GABA to prompt the conversion of a proportion of α cells to an intermediate phenotype (yellow). Further proliferation and redifferentiation replenishes the depleted β cell pool, restoring normal glycemia.

Reference List

