

# A niche mechanism for $\beta$ -cell regeneration in type 1 diabetes

Hodson, David

DOI:

[10.1002/bies.201800177](https://doi.org/10.1002/bies.201800177)

License:

Creative Commons: Attribution (CC BY)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Hodson, D 2018, 'A niche mechanism for  $\beta$ -cell regeneration in type 1 diabetes', *BioEssays*, vol. 40, no. 11, 1800177. <https://doi.org/10.1002/bies.201800177>

[Link to publication on Research at Birmingham portal](#)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

# A Niche Mechanism for $\beta$ -Cell Regeneration in Type 1 Diabetes

David J. Hodson

Type 1 diabetes (T1D) occurs when insulin-secreting pancreatic  $\beta$ -cells are selectively destroyed by immune attack.<sup>[1]</sup> Treatment of T1D therefore requires insulin replacement therapy to enable control over blood glucose levels. While effective, there are issues with injecting insulin, including the loss of protective counter-regulatory responses. Replenishment of endogenous  $\beta$ -cells therefore remains a desirable goal for T1D therapy. However, because  $\beta$ -cell turnover in adults is largely through replication<sup>[2]</sup> and  $\beta$ -cells are lost during T1D, other non- $\beta$ -cell sources need to be identified.

Suggesting that progenitors might be important during islet injury,  $\beta$ -cells renew following diphtheria toxin-mediated ablation.<sup>[3]</sup> Remarkably, these  $\beta$ -cells descend from  $\alpha$ - and  $\delta$ -cells.<sup>[3]</sup> Given that  $\alpha$ -cells persist in T1D islets, this could provide a basis for the restoration of functional  $\beta$ -cell mass. Whether or not similar mechanisms influence  $\beta$ -cell renewal in the absence of manoeuvres to induce profound plasticity has been difficult to assess.

In this issue of BioEssays, Huising et al.<sup>[4]</sup> discuss and expand on recent findings suggesting that plasticity is intrinsic to the unstressed islet. Based on absence of the  $\beta$ -cell maturity marker, urocortin 3 (Ucn3), recent studies have shown the existence of a neogenic niche in adult islets.<sup>[5]</sup>  $\beta$ -cells belonging to the niche occupy the islet periphery, where  $\alpha$ -cells aggregate, and constitute just 1.5% of the total population. These “virgin” cells are insulin+, but are transcriptionally immature and glucose unresponsive. Notably, virgin  $\beta$ -cells were shown to represent an intermediate stage in the transdifferentiation of  $\alpha$ - to  $\beta$ -cells. These findings are important because they suggest that progenitor-like cells with an  $\alpha$ -cell ancestry might give rise to new  $\beta$ -cells.

So how do the authors propose to further test this intriguing hypothesis?  $\beta$ -cells can be labeled using reporter lines, before tracking and quantification. While identical experiments showed

that  $\beta$ -cell renewal is through replication,<sup>[2]</sup> the Cre-driver lines used display poor recombination efficiency, decreasing the power to detect changes. Lineage tracing can also be deployed to determine whether virgin  $\beta$ -cells convert into mature  $\beta$ -cells. To understand the contribution of transdifferentiation to this process, the number of mature (Ucn3+)  $\beta$ -cells with an  $\alpha$ -cell lineage label can be quantified. If the neogenic niche is relevant for T1D, the authors suggest that  $\beta$ -cells possessing an  $\alpha$ -cell lineage label should accumulate in the face of ongoing immune destruction in NOD mouse models.

The proposed studies will provide further mechanistic insight into the role of the neogenic niche in  $\beta$ -cell regeneration. However, lineage tracing has drawbacks. In particular, transgenic  $\alpha$ -cell driver lines can possess variable recombination efficiency and leakiness in different labs. Latest generation CRISPR knock-in animals should help here. It will be interesting to understand how the islet microenvironment influences the niche. This could take the form of experiments in re-aggregated islets where normal  $\alpha$ -/ $\beta$ -cell interactions are lost. Whether or not virgin  $\beta$ -cells give rise to mature  $\beta$ -cells that can proliferate in the face of immune infiltration also needs to be established. Perhaps the most difficult aspect of studying  $\beta$ -cell regeneration, however, is extending findings to humans. While Ucn3-negative  $\beta$ -cells also exist in islets from young donors, their capacity to form new  $\beta$ -cells is unknown. Isolation of these putative virgin  $\beta$ -cells for screening with compound libraries might help identify lead candidates with replicative/proliferative potential. Lastly, the extent to which virgin  $\beta$ -cells can replenish the  $\beta$ -cell complement needs to be established to better demonstrate clinical applicability.

## Conflict of Interest

The author declares no conflict of interest.

Received: September 10, 2018  
 Published online: October 9, 2018

Dr. D. J. Hodson  
 Institute of Metabolism and Systems Research (IMSR)  
 Centre of Membrane Proteins and Receptors (COMPARE)  
 University of Birmingham  
 Birmingham, UK  
 E-mail: d.hodson@bham.ac.uk

Dr. D. J. Hodson  
 Centre for Endocrinology, Diabetes and Metabolism  
 Birmingham Health Partners  
 Birmingham, UK

This article comments on the Hypothesis paper by Mark O. Huising et al. <https://doi.org/10.1002/bies.201800119>

© 2018 The Authors. *BioEssays* Published by WILEY Periodicals, Inc. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1002/bies.201800177

- [1] G. S. Eisenbarth, *N. Engl. J. Med.* **1986**, *314*, 1360.
- [2] Y. Dor, J. Brown, O. I. Martinez, D. A. Melton, *Nature* **2004**, *429*, 41.
- [3] S. Chera, D. Baronnier, L. Ghila, V. Cigliola, J. N. Jensen, G. Gu, K. Furuyama, F. Thorel, F. M. Gribble, F. Reimann, P. L. Herrera, *Nature* **2014**, *514*, 503.
- [4] M. O. Huising, S. Lee, T. van der Meulen, *BioEssays* **2018**, *40*, 180017.
- [5] T. van der Meulen, A. M. Mawla, M. R. DiGruccio, M. W. Adams, V. Nies, S. Dolleman, S. Liu, A. M. Ackermann, E. Caceres, A. E. Hunter, K. H. Kaestner, C. J. Donaldson, M. O. Huising, *Cell Metab.* **2017**, *25*, 911.