COMMENT ON SATIN ET AL.

"Take Me To Your Leader": An Electrophysiological Appraisal of the Role of Hub Cells in Pancreatic Islets. Diabetes 2020;69:830–836

Guy A. Rutter,[1,2] Nikolay Ninov,[3,4] Victoria Salem,[1] and David J. Hodson[5,6,7]

Diabetes 2020;69:e10–e11 | https://doi.org/10.2337/db20-0501

Satin et al. (1) present a critique of a recent model for "hub/follower" dynamics in intra-islet regulation of insulin secretion presented in two recent articles from our laboratories (2,3). Based on older work and our own demonstrations of heterogeneity between individual β-cells, these studies used a combination of multicellular Ca^{2+} imaging, network theory, and interventional approaches to demonstrate that a subpopulation of β-cells within the islet displays earlier responses to stimulation with glucose and is required for fully coordinated behavior across sections of the islet. Studies from others using some of these approaches have reached broadly similar conclusions (4,5).

The critique of Satin et al. (1) is based in large part on estimates of total gap junctional conductance of single β-cells measured using electrode pairs. With the assumption that these values are homogeneous across the islet, they conclude that electrical connectivity would not suffice to transmit signals between cells nor provide a means by which inactivation of a single cell could interfere with signal transmission.

These conclusions suffer from three drawbacks. First, electrical measures of gap junctional conductance are likely underestimated due to series resistance in highly coupled cells and do not fit with recent fluorescence recovery after photobleaching recordings applied to islets (6). Second, extrapolation of measurements to the entire islet may not be valid, since patch-clamp recordings only consider 1–2 cells at once, are prone to misclassification, and suffer from positive selection bias. Third, the authors claim that it would be statistically unlikely for them to have missed one of the so-called hub cells in experiments where individual β-cells were voltage-clamped randomly. Again, this assumption is based on the premises that hub cells are as readily patched as other cells, which is unlikely given their fragility (2), that coupling is homogenous across β-cells, and that islets displaying reduced activity upon voltage clamp would have been taken forward for recording and analysis.

The authors also critique conclusions on gap junction connectivity in zebrafish (3) based on the supposition that Cx35.5 is the only Cx36 ortholog. In fact, its genome encodes four highly conserved Cx36-like proteins. Moreover, zebrafish β-cells are synchronized in vivo, as shown by independent studies, while uncoupling arises specifically upon in vitro culture.

Finally, the authors fail to offer any explanation for our optogenetics, photopharmacology, or photoablation studies (2,3), which demonstrate that clamping the activity of a single cell (or ablating it) restricts the activity of neighboring and more remote cells. We also note that our hypothesis has never claimed that "one cell [could] supply enough current to repolarize the entire islet" (1). Rather, we demonstrate that silencing hub cells dampens activity but more sharply disrupts intercellular connections.

While we welcome the exciting suggestions from Satin et al. (1) of roles for δ-cells and of paracrine factors in

[1]Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, U.K.
[2]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore
[3]Center for Regenerative Therapies at Technische Universität Dresden, Dresden, Germany
[4]Paul Langerhans Institute Dresden of the Helmholtz Center Munich at the University Hospital Carl Gustav Carus, Technische Universität Dresden, German Center for Diabetes Research (DZD), Dresden, Germany
[5]Institute of Metabolism and Systems Research (IMSR), University of Birmingham, Edgbaston, U.K.
[6]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, U.K.
[7]Centre of Membrane Proteins and Receptors (COMPARE), University of Birmingham and University of Nottingham, Midlands, Birmingham, U.K.
Corresponding author: Guy A. Rutter, g.rutter@imperial.ac.uk, or David J. Hodson, d.hodson@bham.ac.uk

β-cell connectivity, we feel it would be premature to discount the involvement of gap junctions, too. As is usual in the scientific method, if a set of assumptions does not readily explain the experimental evidence, one should consider adjustments to the former.

Duality of Interest. G.A.R. has received grant funding from Sun Pharmaceuticals and Les Laboratoires Servier and is a consultant for Sun Pharmaceuticals. No other potential conflicts of interest relevant to this article were reported.

References

1. Satin LS, Zhang Q, Rorsman P. "Take me to your leader": an electrophysiological appraisal of the role of hub cells in pancreatic islets. Diabetes 2020;69:830–836

2. Johnston NR, Mitchell RK, Haythorne E, et al. Beta cell hubs dictate pancreatic islet responses to glucose. Cell Metab 2016;24:389–401

3. Salem V, Delgadillo Silva L, Suba K, et al. Leader β-cells coordinate Ca^{2+} dynamics across pancreatic islets in vivo. Nat Metab 2019;1:615–629

4. Gosak M, Stožer A, Markovič R, et al. Critical and supercritical spatiotemporal calcium dynamics in beta cells. Front Physiol 2017;8:1106

5. Westacott MJ, Ludin NWF, Benninger RKP. Spatially organized β-cell subpopulations control electrical dynamics across islets of Langerhans. Biophys J 2017;113:1093–1108

6. Farnsworth NL, Hemmati A, Pozzoli M, Benninger RK. Fluorescence recovery after photobleaching reveals regulation and distribution of connexin36 gap junction coupling within mouse islets of Langerhans. J Physiol 2014;592:4431–4446