Investigating β-cell Functional Heterogeneity in Zebrafish Using Single-Cell Optogenetics

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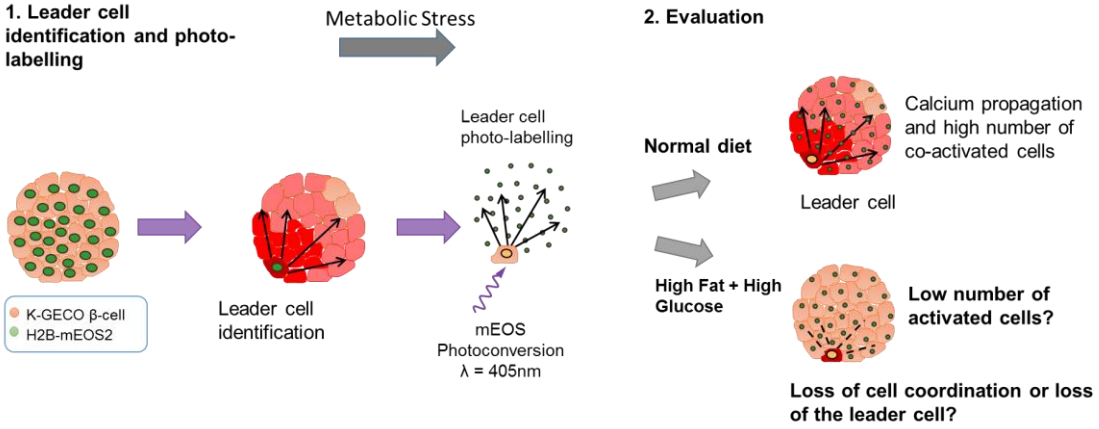
Leader β-cells coordinate Ca^{2+} dynamics *in vivo*.

There is emerging evidence that the pancreatic beta-cells are heterogeneous and form subpopulations with distinct characteristics. It is believed that individual beta-cells specialize towards performing specific tasks in the islet (e.g. proliferation versus function), which might increase the overall fitness of the cellular community. However, the origins and the role of cell heterogeneity in islet physiology and pathophysiology are yet to be defined. Recently, we identified a critical subpopulation of β-cells, called leader cells, which guide the response of the rest of cells to glucose[1]. When we destroyed precisely the leader cells using photo-ablation, the coordinated islet activity was immediately impaired. In a close collaboration with Prof. Guy Rutter (Imperial College London), we applied high-speed *in vivo* 3D Ca^{2+} imaging and novel analytical approaches to reveal that the leader β-cells are the first cells to respond to glucose in both zebrafish and mouse islets. Critically, islet coordination was aberrant in human islets taken from subjects with T2DM. This led us to put forward the concept that leader cells are selectively affected during diabetes progression, leading to islet dysfunction. **Thus, the current working model is that the loss of a critical subpopulation of β-cells may impair the function of islets trough disrupted Ca^{2+} responses.**

To understand the role of this functional heterogeneity for insulin secretion, my group has developed unique state-of-the-art tools to study and manipulate β-cell function[1-5]. Among our newest tools are transgenic lines with β-cell-specific expression of optogenetic effectors, as well as methods to photo-label and track over time single cells in the islet. Using our new technologies, we propose to address fundamental questions related to the development of leader cells within islets, their stability and metabolic signatures, as well as to define novel molecular markers of leader and follower cells. Moreover, we will apply the new tools to study how leader cells are affected by β-cell stress, either metabolic or inflammatory, and to find out if leader-cells can die or lose their function under such conditions. Addressing these fundamental questions will be paramount to understand why type 2 diabetic islets show normal β-cell mass but impaired cell-coordination and islet function. A possible explanation is that the loss of leader cells prevents the proper functioning of the islets. If this turns out to be the case, new strategies aiming to protecting and restoring leader cells will be necessary.



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