Islet on a Chip – Metabolic Control of Beta Cells by the Extracellular Matrix

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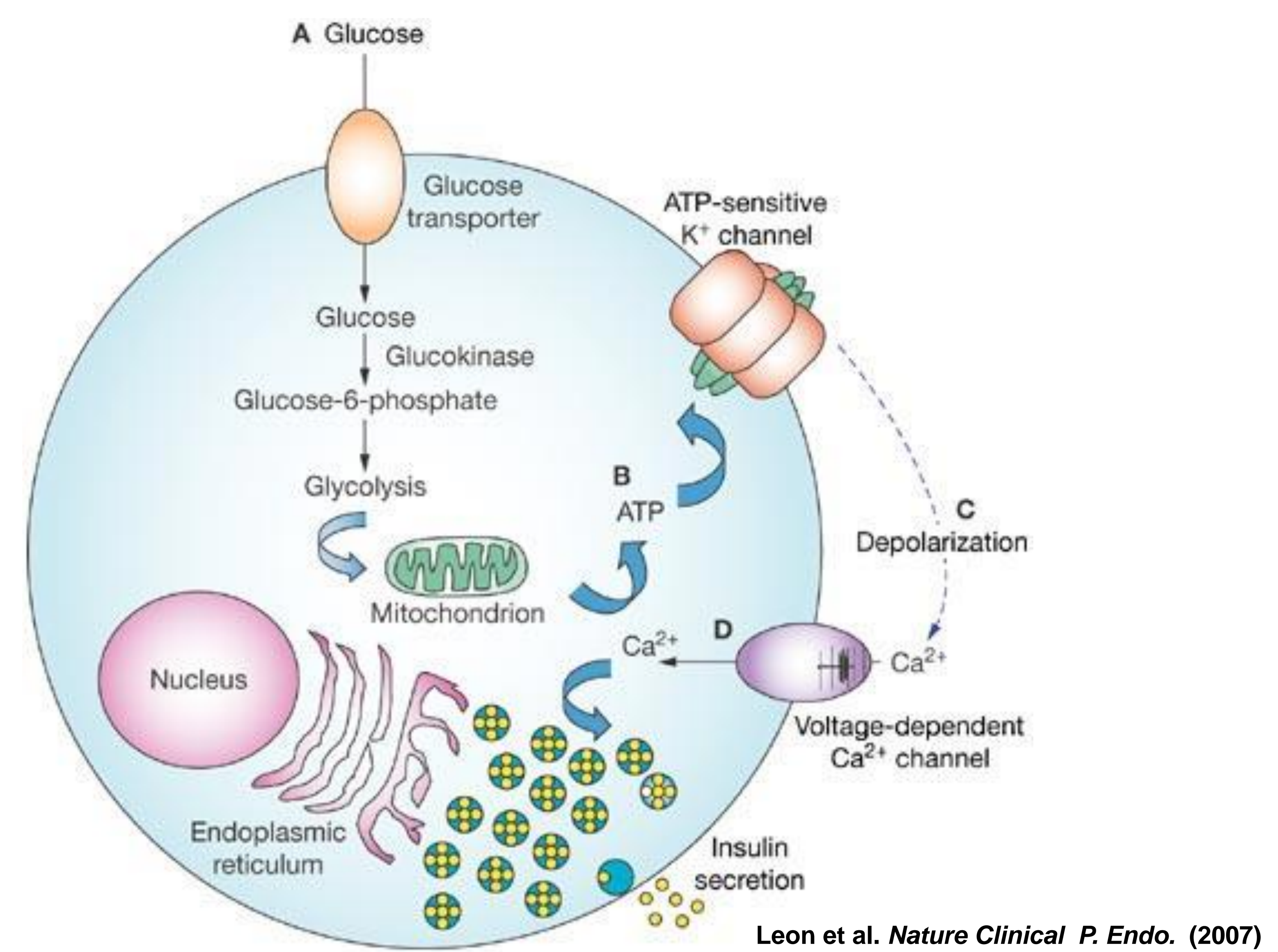
Background

Problem: Diabetes results from inadequate insulin production or improper responses to the insulin produced. Research access to human pancreatic beta cells, the body's natural source of insulin, has been restricted to cadavers that are limited in number, sporadic in availability, and inherently variable due to the circumstances in which they are obtained. Moreover, cadaveric beta cells maintained in vitro lose functionality within days, challenging the physiological relevance of culture conditions. To meet demands of the rising global incidence of diabetes (9% of adults as of 2014), scientists would benefit from access to more predictable sources of human beta cells and culture conditions that maintain beta cell functionality.

Hypothesis: The physical properties of tissue-specific microenvironments vary widely in the human body and demonstrably influence the structure and function of many cell types. Despite this demonstration, *in vitro* human cell culture is mainly performed on relatively stiff polystyrene, limiting the clinical relevance of data obtained from cultured cells. We hypothesize that recapitulating the composition and mechanical properties of the native extracellular matrix will promote the functionality of beta cells cultured in vitro.

Approach: We recently generated beta cells from human pluripotent stem cells. To complement this unlimited, defined source of human beta cells for research applications, we are designing an in vitro platform that mimics the extracellular matrix of native pancreatic islets. Beta cells regulate circulating glucose levels by secreting insulin in response to increases in intracellular glucose metabolism. To assay metabolism in beta cells, we are quantifying basal and glucose stimulated oxygen consumption and extracellular acidification rates as a proxy for intracellular glucose metabolism and subsequent insulin secretion.

Outcome: We are identifying aspects of the extracellular matrix that control beta cell metabolism. These results inform the design of our in vitro platform to maintain functionality of cultured beta cells.



Cellular Mechanism of Insulin Release of Pancreatic Beta Cell.
Glucose is transported across the cell membrane (A). Glycolytic ATP production (B) initiates a signaling cascade that closes K-ATP sensitive ion channels. The resulting membrane depolarization (C) triggers influx of calcium through L-type calcium channels (D) required for insulin release.

Main Achievements

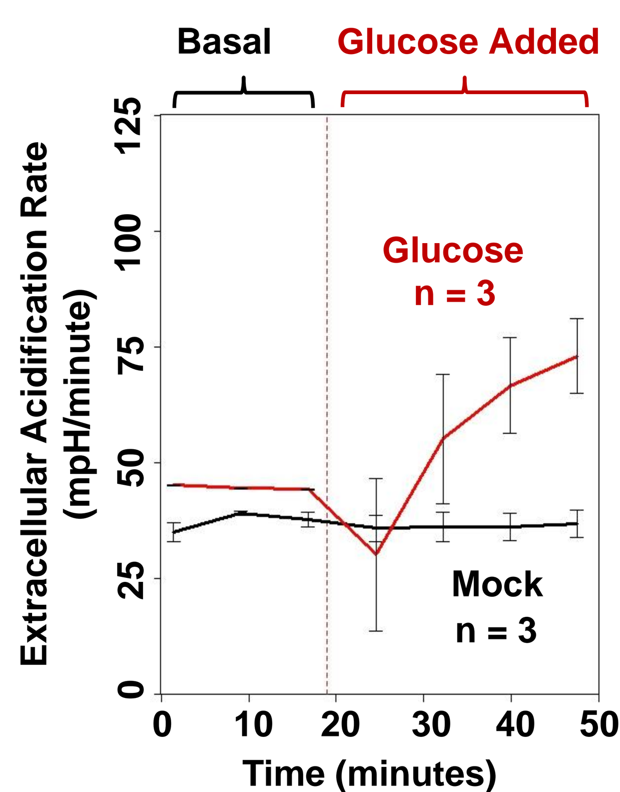


Figure 1 | Extracellular acidification rates in a time course before and after glucose stimulation of SC-beta cells.

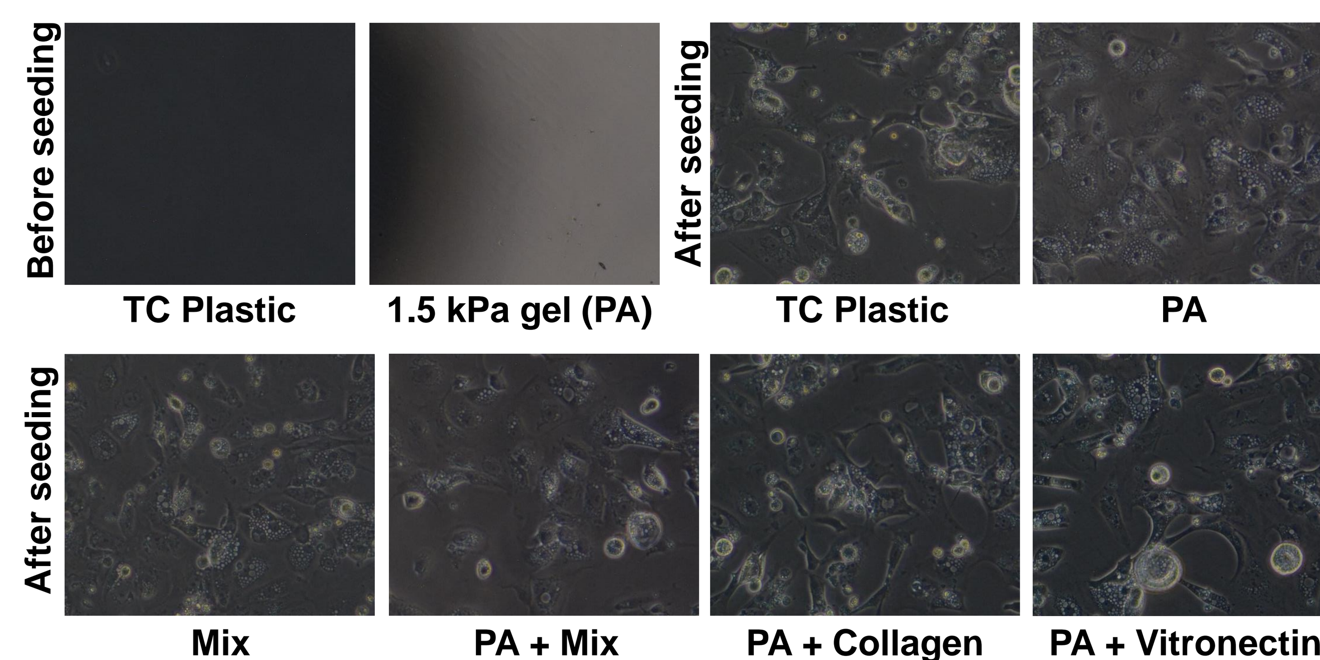


Figure 2 | Phase contrast microscopy of SC-beta cells cultured on different growth substrates.

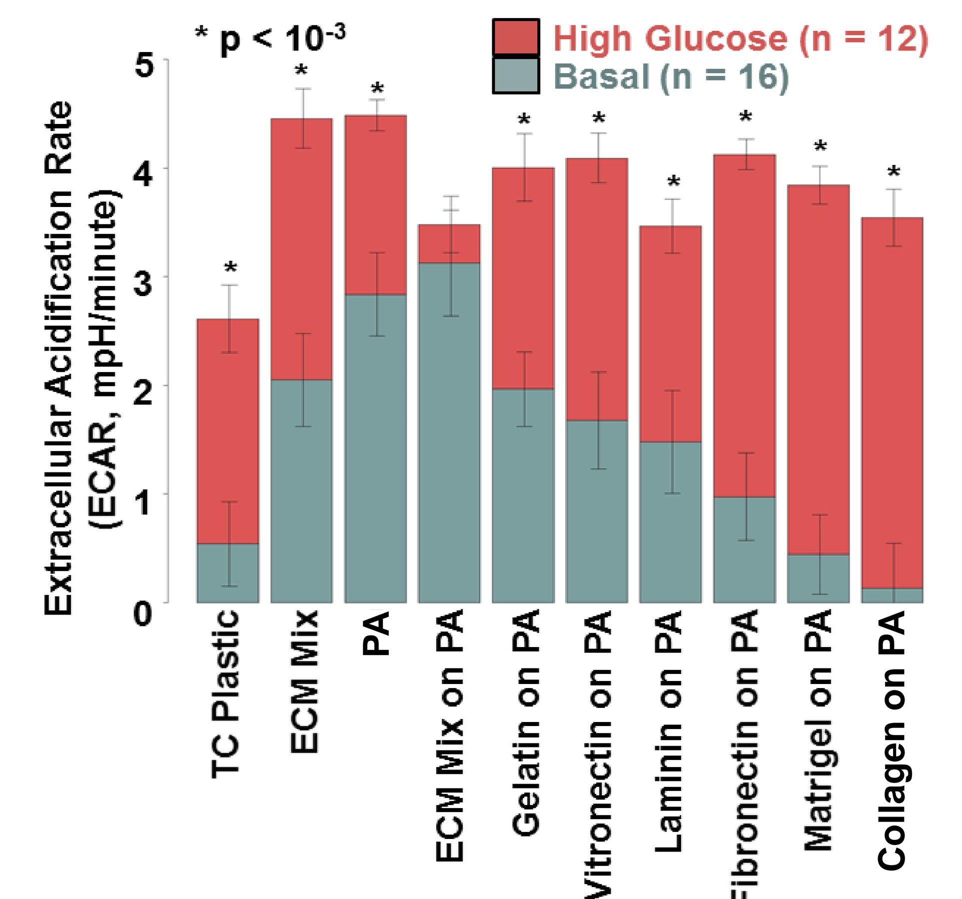


Figure 3 | Extracellular acidification rates in glucose stimulated SC-beta cells cultured on different growth substrates.

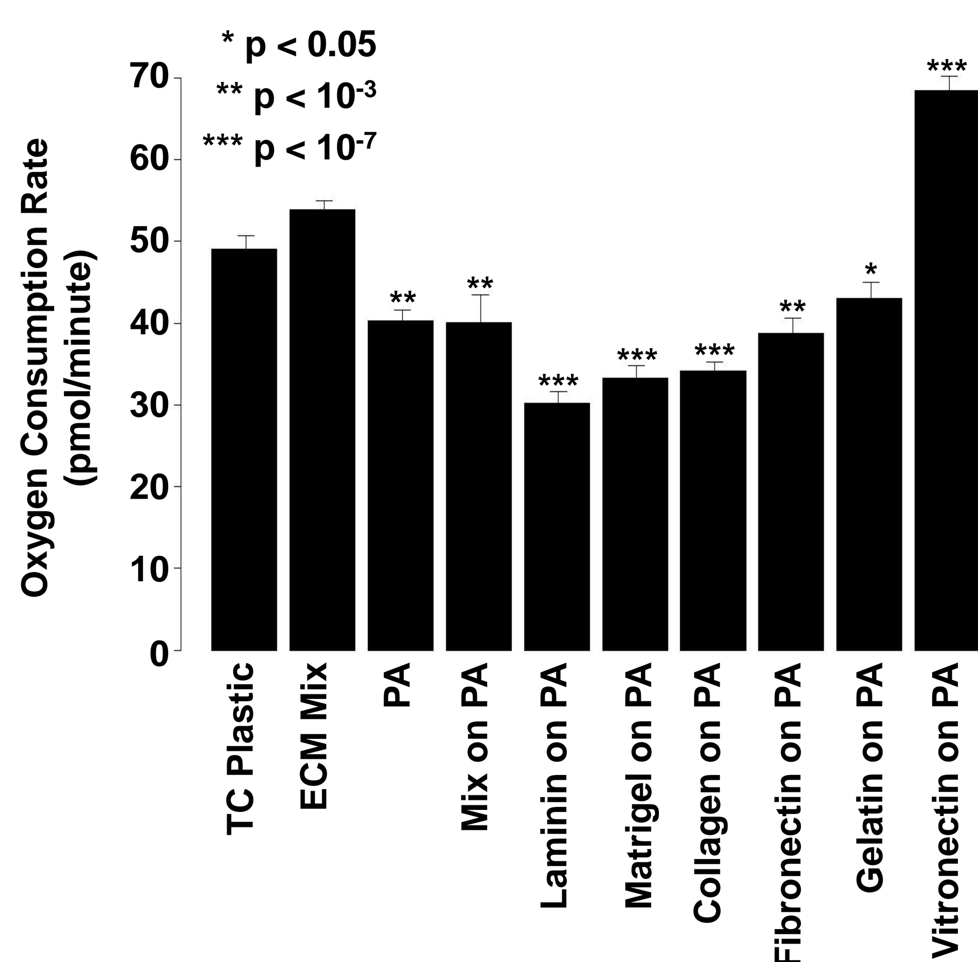


Figure 4 | Basal oxygen consumption rates in SC-beta cells cultured on different growth substrates. One-way ANOVA was used for statistical analysis. n = 16.

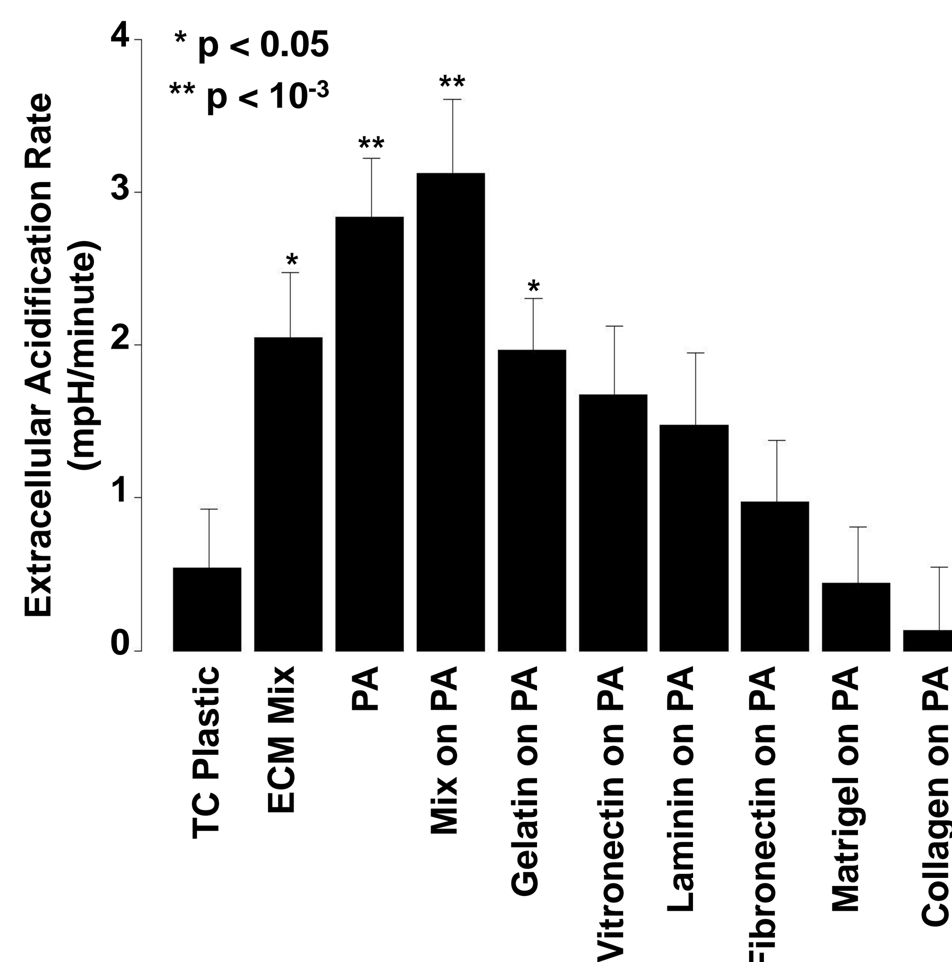


Figure 5 | Basal extracellular acidification rates in SC-beta cells cultured on different growth substrates. One-way ANOVA was used for statistical analysis. n = 16.

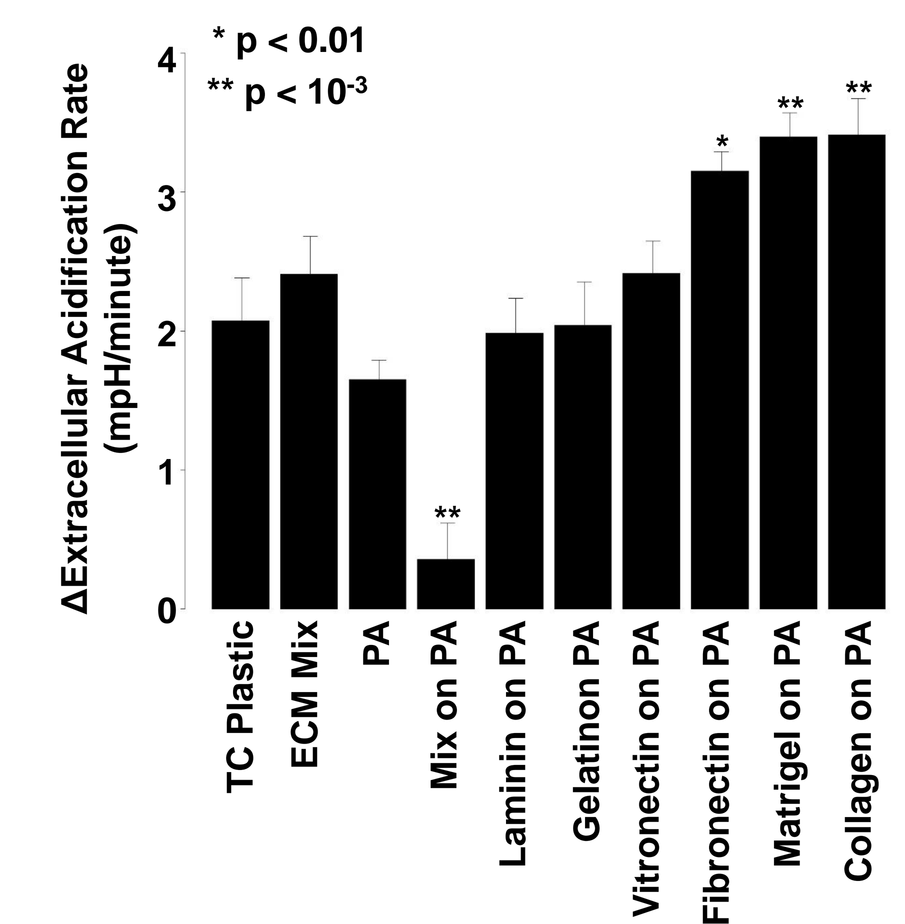


Figure 6 | Increases in extracellular acidification rates in glucose stimulated SC-beta cells cultured on different growth substrates. One-way ANOVA was used for statistical analysis. n = 12.

Future Directions

The results of our metabolic assays from beta cells cultured on growth substrates that mimic the native extracellular matrix demonstrate regulation of beta cell glucose metabolism by the extracellular matrix. We are now investigating the mechanism by which signals from the ECM are transduced to control glucose metabolism and we will use these results to inform the design of our in vitro platform to maintain functionality of cultured beta cells.

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NIH National Institute of Diabetes and Digestive and Kidney Diseases