Molecular interplay between α- and β-cellular clocks: roles in the islet physiology and pathophysiology

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Peripheral clocks control the body metabolism

- In mice, direct connection between clock disfunction (genetic knock out models) and overt type 2 diabetes development has been established (Marcheva et al., Nature 2010; Perelis et al., Science 2015)
Methods

A

[Diagram showing diurnal cycle with time points ZT0 to ZT20 and food accessibility]

B

[Diagram showing blood sample collection, islets isolation, FACS separation, and RNAseq/qPCR analysis for α-cells and β-cells]
Results I. Mouse model
α- and β-cellular clocks differentially regulate transcriptome and islet hormone secretion

Petrenko et al., submitted to Genes and Development
Results II. Human model
Circadian clock operative in human islet regulates insulin secretion and islet gene transcription

Number of genes changed

Bioluminescence (counts/min)

% of secreted insulin from total secretion

Saini et al., Diabetes, Obesity and Metabolism, 2016
Conclusions

• In mouse model, α- and β-cellular clocks exhibit distinct molecular makeup and differentially regulate gene transcription and islet hormone secretion

• Clock disruption in adult human pancreatic islet leads to disrupted insulin secretion and to alterations in the islet transcriptome, including key genes in insulin secretory pathway (Saini et al., 2016)

• We are able to characterize the oscillator molecular makeup in human T2D islets (not shown)
Questions raised and importance

1. Is the circadian clock perturbed in type 2 diabetic patients?
2. If so, is there a way to fix it?