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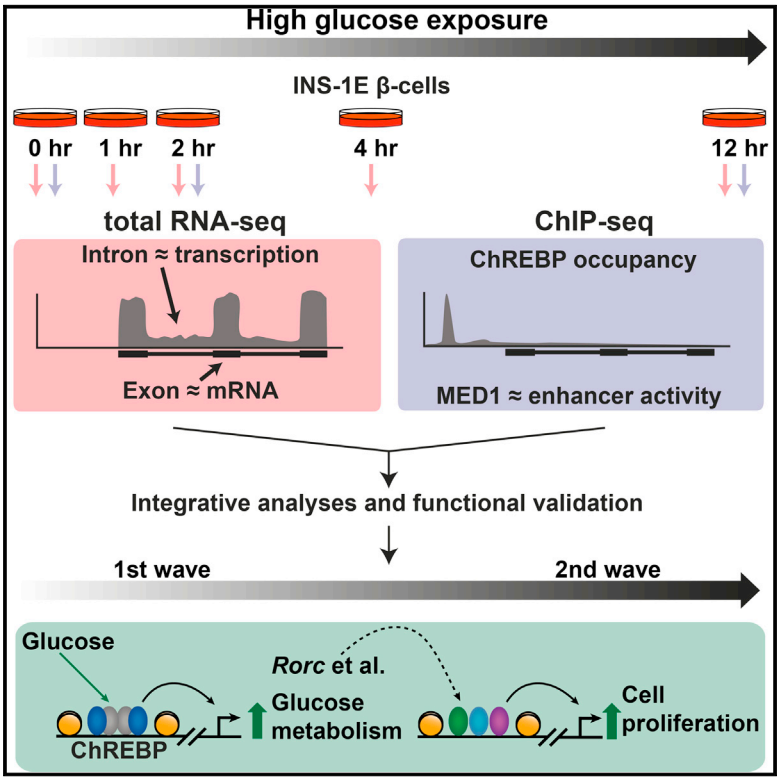
Integrative Genomics Outlines a Biphasic Glucose Response and a ChREBP-RORγ Axis Regulating Proliferation in β Cells

Graphical Abstract



Highlights

- Glucose reprograms the transcriptional network of INS-1E β cells in a biphasic manner
- ChREBP is a central regulator of the first wave of the glucose response
- Induction of cell-cycle genes requires ChREBP-induced transcription factors
- RORγ is required for full glucose-induced proliferation of INS-1E and primary β cells

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In Brief

Schmidt et al. characterize the transcriptional reprogramming of the β cell enhancer and gene landscape by glucose and outline a ChREBP-initiated, biphasic response. Delayed induction of cell-cycle genes is mediated by secondary transcription factors including RORγ, which is required for full induction of β cell proliferation by glucose.

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Integrative Genomics Outlines a Biphasic Glucose Response and a ChREBP-RORγ Axis Regulating Proliferation in β Cells

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SUMMARY

Glucose is an important inducer of insulin secretion, but it also stimulates long-term adaptive changes in gene expression that can either promote or antagonize the proliferative potential and function of β cells. Here, we have generated time-resolved profiles of enhancer and transcriptional activity in response to glucose in the INS-1E pancreatic β cell line. Our data outline a biphasic response with a first transcriptional wave during which metabolic genes are activated, and a second wave where cell-cycle genes are activated and β cell identity genes are repressed. The glucose-sensing transcription factor ChREBP directly activates first wave enhancers, whereas repression and activation of second wave enhancers are indirect. By integrating motif enrichment within late-regulated enhancers with expression profiles of the associated transcription factors, we have identified multiple putative regulators of the second wave. These include RORγ, the activity of which is important for glucose-induced proliferation of both INS-1E and primary rat β cells.

INTRODUCTION

Pancreatic β cells play a key role in the regulation of glucose uptake and metabolism. They respond to a rise in blood glucose by increasing the secretion of insulin, which in turn increases the storage and utilization of glucose in peripheral tissues. Type 2 diabetes (T2D) is caused by an inability of the β cells to secrete sufficient amounts of insulin to meet the demands for nutrient use and storage. Insulin resistance in liver and peripheral tissues contributes significantly to this imbalance, but whether insulin resistant subjects develop hyperglycemia appears to depend on their ability to expand the β cell mass or capacity in response to the increased metabolic load. Conversely, β cells of type 2 diabetics respond poorly to a glucose challenge; however, the etiology of β cell dysfunction in T2D remains controversial. Traditionally, the deficit in β cell capacity has been ascribed to increased apoptosis, but recent studies suggest that β cell dedifferentiation plays a dominant role in β cell failure in T2D (Talchai et al., 2012). Interestingly, during the progression to insulin resistance and T2D, it appears that glucose itself acts both to promote expansion of β cell mass to meet higher demands of insulin (Levitt et al., 2011; Lingohr et al., 2002) and as a stressor that can lead to dysfunction, so-called glucotoxicity (Brun et al., 2015; Prentki and Nolan, 2006). However, so far the changes in β cell gene expression underlying these adaptive and pathogenic effects are far from understood, and genome-wide insight into transcriptional reprogramming of the β cell genome by glucose is missing.

Several recent studies have implicated the transcription factor carbohydrate response element binding protein (ChREBP) in glucose-induced regulation of β cell gene expression and function (Boergesen et al., 2011; da Silva Xavier et al., 2006; Metukuri et al., 2012; Poungvarin et al., 2012). ChREBP is a basic helix-loop-helix leucine zipper (bHLH-LZ) transcription factor that exerts its actions by binding to DNA on carbohydrate response elements (ChoREs) together with another bHLH-LZ protein called Max-like protein X (Mlx) (Ma et al., 2005). ChREBP senses glucose by multiple different mechanisms, which vary between cell types, but most signaling converge onto a glucose sensing module in the N terminus, the deletion of which renders ChREBP