Epigenetics of Pancreatic Alpha- and Beta-Cells - Potential for New Therapeutics for Diabetes?

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Insulin-secreting β cells and glucagon-secreting α cells maintain physiological blood glucose levels, and their malfunction drives diabetes development. Using ChIP sequencing and RNA sequencing analysis, we determined the epigenetic and transcriptional landscape of human pancreatic α, β, and exocrine cells. We found that, compared with exocrine and β cells, differentiated α cells exhibited many more genes bivalently marked by the activating H3K4me3 and repressing H3K27me3 histone modifications. This was particularly true for β cell signature genes involved in transcriptional regulation. Remarkably, thousands of these genes were in a monovalent state in β cells, carrying only the activating or repressing mark. Our epigenomic findings suggested that α to β cell reprogramming could be promoted by manipulating the histone methylation signature of human pancreatic islets. Indeed, we show that treatment of cultured pancreatic islets with a histone methyltransferase inhibitor leads to colocalization of both glucagon and insulin and glucagon and insulin promoter factor 1 (PDX1) in human islets and colocalization of both glucagon and insulin in mouse islets. We are now developing tools for the cell-type and locus-specific epigenetic reprogramming of key transcription factors such as MAFA, PDX1, and ARX, using fusion proteins of TALE-DNA binding domains with the catalytic domains of chromatin modifiers. Thus, mammalian pancreatic islet cells display cell-type-specific epigenomic plasticity, suggesting that epigenomic manipulation could provide a path to cell reprogramming and novel cell replacement-based therapies for diabetes.