A139 · Mapping Cis-Regulatory Programs of Pancreatic β Cells in Health and Diabetes

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Pancreatic β-cell dysfunction is central to both type 1 (T1D) and type 2 diabetes (T2D), yet the regulatory programs underlying β-cell identity and failure remain incompletely characterized. The scarcity of primary human pancreatic tissue has further limited our ability to define β-cell and other endocrine cell states. Despite numerous efforts to profile chromatin accessibility in human islets, these datasets remain fragmented across studies and biological contexts, limiting a systematic view of the pancreatic regulatory landscape.

To address this gap, we systematically collected and uniformly processed over 20 publicly available bulk and single-cell chromatin accessibility datasets comprising more than 250 human donors. Using a standardized framework based on ENCODE protocols, we constructed a unified map of candidate cis-regulatory elements (cCREs) across pancreatic endocrine (β, α, and δ) and exocrine cell types. This resource spans healthy, prediabetic, T1D, and T2D states, as well as ex vivo perturbation models that mimic disease-relevant conditions, including inflammation and endoplasmic reticulum stress.

We expanded the pancreatic regulatory landscape at cell-type resolution, identifying thousands of cCREs selectively accessible in β cells across diabetic and stress conditions. Importantly, we recovered additional cCREs absent from the existing ENCODE registry, many selectively active in endocrine and disease-associated states, suggesting that these rare contexts remain underrepresented in existing references. Applying sequence-based deep learning models of chromatin accessibility, we further nominated regulatory sequence features and candidate transcription factors that distinguish β cells in disease-relevant states. Together, this resource provides a more complete picture of β-cell regulation in the context of diabetes.