

Formation of a Baseline Pancreatic β -cell Mass in Humans is Completed Early in Life

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Purpose: The baseline complement of pancreatic islet beta cells in an individual can be pivotal in the pathogenesis of diabetes. In type 1 diabetes, it may predict the extent of an autoimmune attack. In type 2 diabetes, it can dictate whether beta cell mass can compensate, or not, in the face of an increased metabolic load/insulin resistance. However, there have been a limited number of studies in humans and it is unclear how, and when, a baseline beta cell mass forms. Moreover, since a fully functional beta cell requires interaction with other islet hormone producing cell types and associated cells (e.g., neuronal cells), the formation of normal human beta cell mass relative to other pancreatic cell types is important. Here we have examined the formation of normal human beta cell mass relative to alpha-, delta-, and pancreatic neuronal cells from late development, neonatal, childhood, adolescent through to adulthood.

Methods: Pancreatic sections (10 μ m thick) were analyzed by immunofluorescent staining and confocal microscopy for the formation of alpha-(glucagon), beta-(insulin), delta-(somatostatin) cells relative to each other. Ductal (CK-19) and beta cell proliferation was examined by Ki67 staining and apoptosis by activated caspase-3. The neogenesis of beta cells (insulin+ cell emerging from or associated to pancreatic ductal cells) was also assessed. The formation neurons proximal to pancreatic islet beta cells was examined using TUJ1/MAP2 as a neuronal specific marker. Each section was quantified by morphometric counting analysis.

Summary of Results: The baseline pancreatic beta cell mass was formed early in neonatal human life. This was a result of beta cell neogenesis mostly occurring developmentally and then a burst of neonatal beta cell proliferation, which doubled the beta cell population by age 2 years. Thereafter, the beta cell population stayed relatively constant with very low levels of neogenesis, proliferation and apoptosis. The pancreatic alpha and delta-cell populations appeared to be set at birth. The beta cell:alpha-cell ratio approximately doubled in the first year of life – reflective of the burst of beta cell proliferation rather than change in alpha-cell numbers. The beta cell:delta-cell ratio changed more dramatically (~8-fold) through childhood from birth reflecting a marked loss of delta-cells in the first 10 years of life. A neonatal burst of ductal cell proliferation was also observed that followed the burst of beta cell proliferation, and was more likely associated with expansion of pancreatic exocrine cells as formation of pancreatic islets occurred. Finally, it was found that $\geq 90\%$ of detectable pancreatic neurons first associated with pancreatic endocrine islet beta cells developmentally, and this tight association was retained throughout adulthood. Few pancreatic neurons associated with exocrine tissue.

Conclusions: The baseline complement of human pancreatic islet beta cells is set early, by ~2 years old. There is a tight association of neurons and pancreatic alpha-cells to islet beta cells, but islet delta-cells are lost during childhood. This study has implications to intra-uterine fetal programming having influence on the formation of baseline beta cell mass, and, if dysfunctional, could contribute to the pathogenesis of diabetes later in life.