Normal Regulation of Pancreatic Function

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Blood Glucose is a Function of:

- Insulin Level
- Glucose Disposal
- Glucose Production
Glucose Homeostasis

Muscle, Fat

Pancreatic Islet

Insulin, Glucagon

Glucose production, storage

Glucose utilization

Liver

Glucose
Intravenous Glucose Tolerance Test

Overview

- Pancreas morphology
- Islet vasculature and innervation
- Pancreas development
- Insulin biosynthesis
- Intercellular contacts within islets
- Regulation of insulin and glucagon secretion
- Approaches to study islet function
Pancreas in situ

It is located behind the stomach and is covered by the transverse mesocolon so it is 2° retroperitoneal

Other relations:
It is hugged by the duodenum and its tail tickles the spleen
Pancreas is Mixed Exocrine and Endocrine Organ

• sg - secretory granules
• zg - zymogen granules
• ER - endoplasmic reticulum
• N - nucleus

islet cells

exocrine cells
Islet Endocrine Cells Have Distinct Secretory Granules

α cell

β cell

δ cell
Islets are Highly Vascularized Mini-organs

Islet in Mouse Pancreas

Endothelial cells (Lectin-FITC)

Angiogenic Factors

- Basic FGF
- Angiopoietin Family
- Ephrin Family
- VEGF Family
β Cell-Specific Inactivation of VEGF Results in Reduced Islet Vasculature

VEGF$^{fl/fl}$

Rip-Cre;VEGF$^{fl/fl}$

CD31/δ cells

Islet Capillaries are Fenestrated

Cleaver, O. and Melton, D., Nat. Med., 2003
Islet Capillaries Have More Fenestrations Than Those in Exocrine Tissue

- **Islets** - 1.3 fenestrae/1 μm endothelium
- **Exocrine tissue** - 0.13 fenestrae/1 μm endothelium

Islets Have Direct Arterial Supply

- Islets receive 10 fold more blood flow than acinar tissue (5-15% of pancreatic blood flow).

Takuro M. et al., Microscopy Research & Technique, 1997

Cleaver, O. and Melton, D., Nat. Med., 2003
Islets are Highly Innervated

- Islets receive sympathetic (NPY), parasympathetic (Ach, VIP) and sensory nerve fibers (CGRP)
- Innervation is important for islet function

Courtesy of Rachel Reinert
Nerves and Blood Vessels Are Closely Associated

Limb skin

SEM micrograph of pancreatic islet

Adopted from Carmeliet et al., 2005
Sunami et al., 2001
Pancreas Develops as Evaginations of Primitive Gut Epithelium

Pancreatic Exocrine and Endocrine Cells Share Common Heritage

Figure - M Gannon, adapted
Events of Pancreatic Organogenesis

Jensen J., Developmental Dynamics, 2004
Kim and MacDonald, Curr Opin Genet Dev, 2002
Reciprocal Endothelial-Endocrine Cell Signaling During Pancreatic Development

- Endothelial cells play a critical role in specification and differentiation of early pancreatic endoderm.
  
  *Lammert E et al.: Science 294:564-567, 2001*
  
  *Yoshitomi H, Zaret KS: Development 21:21, 2004*

- Functional blood vessels are required for subsequent steps of pancreatic development (formation of mesenchyme, dorsal bud outgrowth).
  

VEGF-A Expression Pattern in Developing Pancreas

dorsal pancreas at e16.5