\[\beta \text{ Cell Clusters in Normal Developing Pancreas}\]
Possible Sources Of New Islet Cells.....

3. Multipotent Precursors
   (e.g. Adult Stem Cells)

   Isolation
   Expansion
   Differentiation

4. Pluripotent Stem Cells
   (e.g. ES cells)

   Replacement
   β cells/islets

1. β cells
   (human)

2. Porcine islets

Figure - M Gannon, adapted
Insulin Biosynthesis

- **Nucleus**
  - mRNA

- **Ribosome**
  - rER

- **Golgi**
  - Cis Golgi
  - Proinsulin vesicles

- **Trans Golgi**

- **Preproinsulin**
  - SP (24)
  - B chain (30)
  - C peptide (31)
  - A chain (20)

- **Proinsulin**
  - SP cleaved
  - Folding
  - Forming disulfide bonds

- **Cleavage of proinsulin**
  - PC1: Arg31/Arg32
  - PC2: Lys64/Arg65

- **Insulin**
  - C peptide
β Cells are Coupled by Gap Junctions

- Allow direct cell-to-cell communication
- 6 Cx molecules form connexon
- β Cells are coupled by Cx36 gap junctions
- Connexons of adjacent cells form junctional channels
- Permeable to molecules up to 1 kD
Gap Junctions Interact with Tight Junctions in $\beta$ Cell Membrane

- **sg** – secretory granules
- **gj** – gap junctions
- **tj** – tight junctions
- **mv** – microvilli

Freeze fracture replica

Orci L., Experintia, 1973
Regulators of Insulin Secretion

- **Nutrients**
  - Glucose (+)
  - Amino Acids (+)
  - Keto acids (+)

- **GI Hormones**
  - GLP-1 (+)
  - GIP (+)
  - Gastrin, CCK (+)

- **Nerves**
  - Sympathetic (-)
  - Parasympathetic (+)

- **Other Hormones**
  - Glucagon (-)
  - Epinephrine (-)
  - Growth Hormone (+)
  - Somatostatine (-)
Regulation of Insulin Secretion

Two Phases of Insulin Secretion

Adapted from Owen McGuinness
Insulin

- $T^{1/2} = 5-8$ minutes, 5800 D protein
- Secreted into portal vein
- Metabolized by liver (50%) and peripheral tissues
- Co-secreted with C-peptide which has much longer half-life but no known function
- Co-secreted with amylin (Islet associated pancreatic polypeptide (influences GI motility))
Oral Glucose vs IV Glucose

“Incretin” effect

Washington University, on-line
“Incretins” - Released from GI Tract

GLP-1
GIP

Food ingestion

GI tract

Intestinal secretion of GLP-1(7-36)amide and GIP(1-42)

Incretin action

Liver

10-15% of secreted amount leaves liver
25% reaches liver

Villus

L-cell

100% secreted

DPP-IV breakdown

Gastroenterology 132:2131, 2007
Physiol Rev. 2007 Oct;87(4):1409-39
Insulin Secretion

Reciprocal Insulin and Glucagon Secretion

Guyton and Hall Textbook
Regulators of Glucagon Secretion

• Positive
  – Hypoglycemia
  – Sympathetic nervous system
  – Amino acids
  – Stress
  – Exercise

• Negative
  – Somatostatin
  – Insulin
  – Hyperglycemia
Glucagon Gene and Protein
Glucagon

- 29 amino acids
- $T\frac{1}{2} = 5$ minutes
- Secreted into portal vein
- Metabolized by liver (75%) and kidney
- Opposes action of insulin and elevates blood glucose
- Promotes glycogenolysis and gluconeogenesis
How do I dissect defects in islet function?
Cell Inactivation of VEGF-A Impairs Glucose Tolerance

\[ \text{Blood glucose (mg/dL)} \]

\[ \text{Insulin/glucose (ng/g)} \]

**Age:** 10 - 14.7 wk

- VEGF\(^{fl/fl}\), \( n = 26 \)
- Rip-Cre;VEGF\(^{fl/wt}\), \( n = 14 \)
- Rip-Cre;VEGF\(^{fl/fl}\), \( n = 22 \)
- Rip-Cre;VEGF\(^{wt/wt}\), \( n = 7 \)

Brissova et al., Diabetes, 2006

- 15 min after glucose administration
Schematic of Islet Perifusion Apparatus

- Utilizes diffusion delivery of islet stimuli
Insulin Secretion is Normal in VEGF-A Deficient Isolated Islets

Brissova et al., Diabetes, 2006
Pancreas Perfusion *in situ*

- Utilizes native vasculature of the pancreas for delivery of islet stimuli
β Cell Inactivation of VEGF-A Impairs Vascular Delivery of Insulin

Pancreas Perfusion

*in situ*

- VEGF\(^{fl/fl}\), \(n = 5\)
- Rip-Cre;VEGF\(^{fl/fl}\), \(n = 5\)

Brissova et al., Diabetes, 2006
Is my pancreas abnormal? Evaluating pancreatic function

- GTT (L-arginine response)
- ITT
- Glucose stimulated insulin secretion (GSIS) \textit{in vivo} plus stimuli that converge with different steps of GSIS
- Islet morphology (islet cell distribution)
- Islet mass
- Pancreatic/islet insulin content
- Insulin secretion \textit{in vitro} (islet perifusion, pancreas perfusion)