

Investigating Fetal Pancreatic β -cell NF κ B Signaling as a Novel Pathway Linking Early Metabolic Dysfunction to Type 2 Diabetes Later in Life

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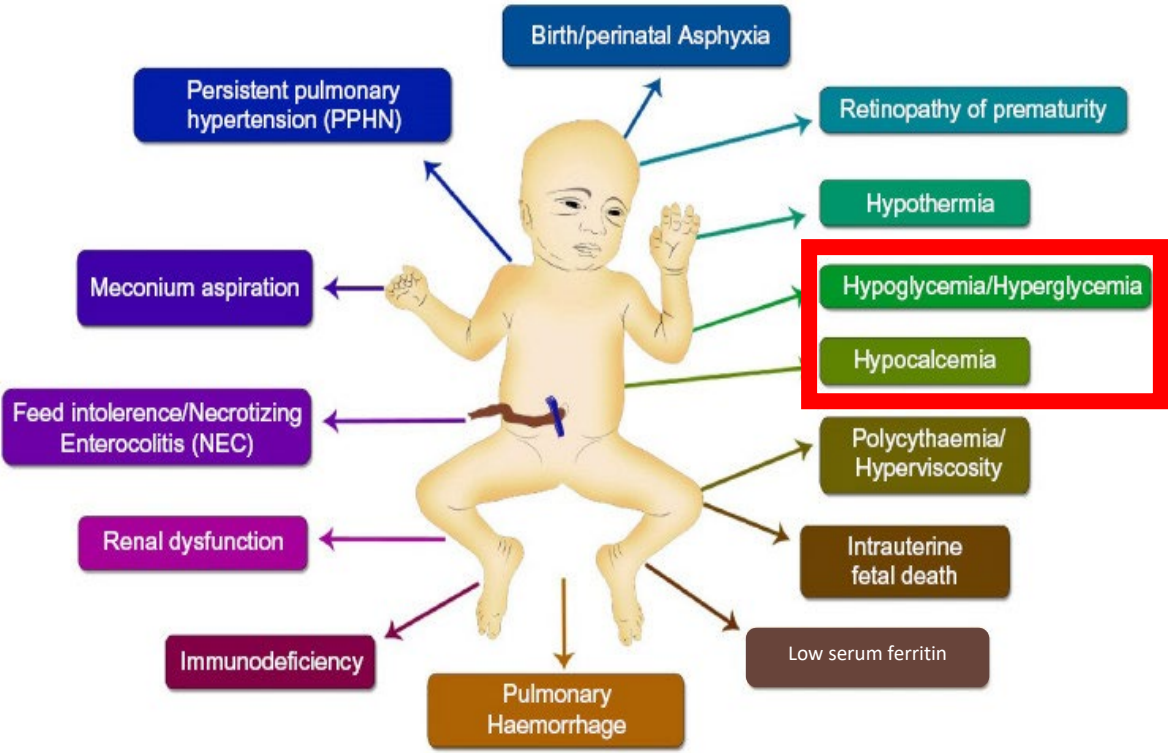
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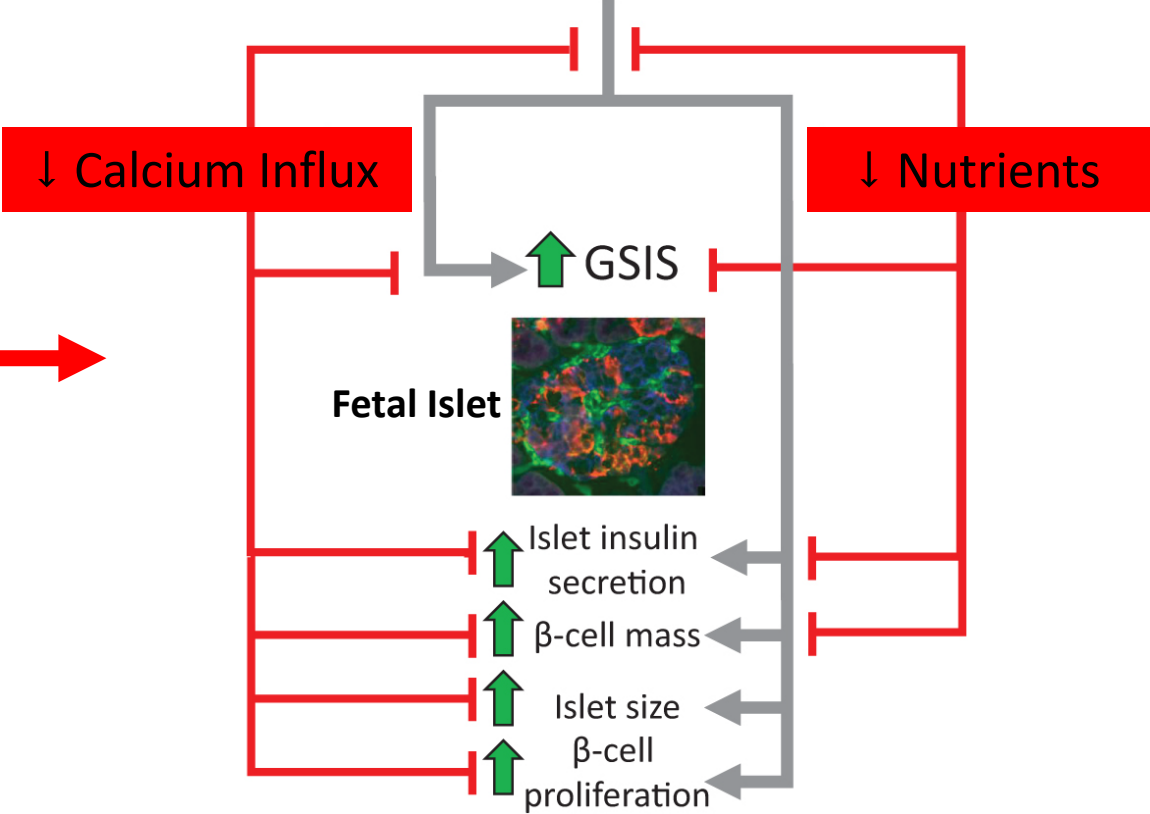
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Fetal growth restriction is common and results in long-term metabolic consequences including type 2 diabetes

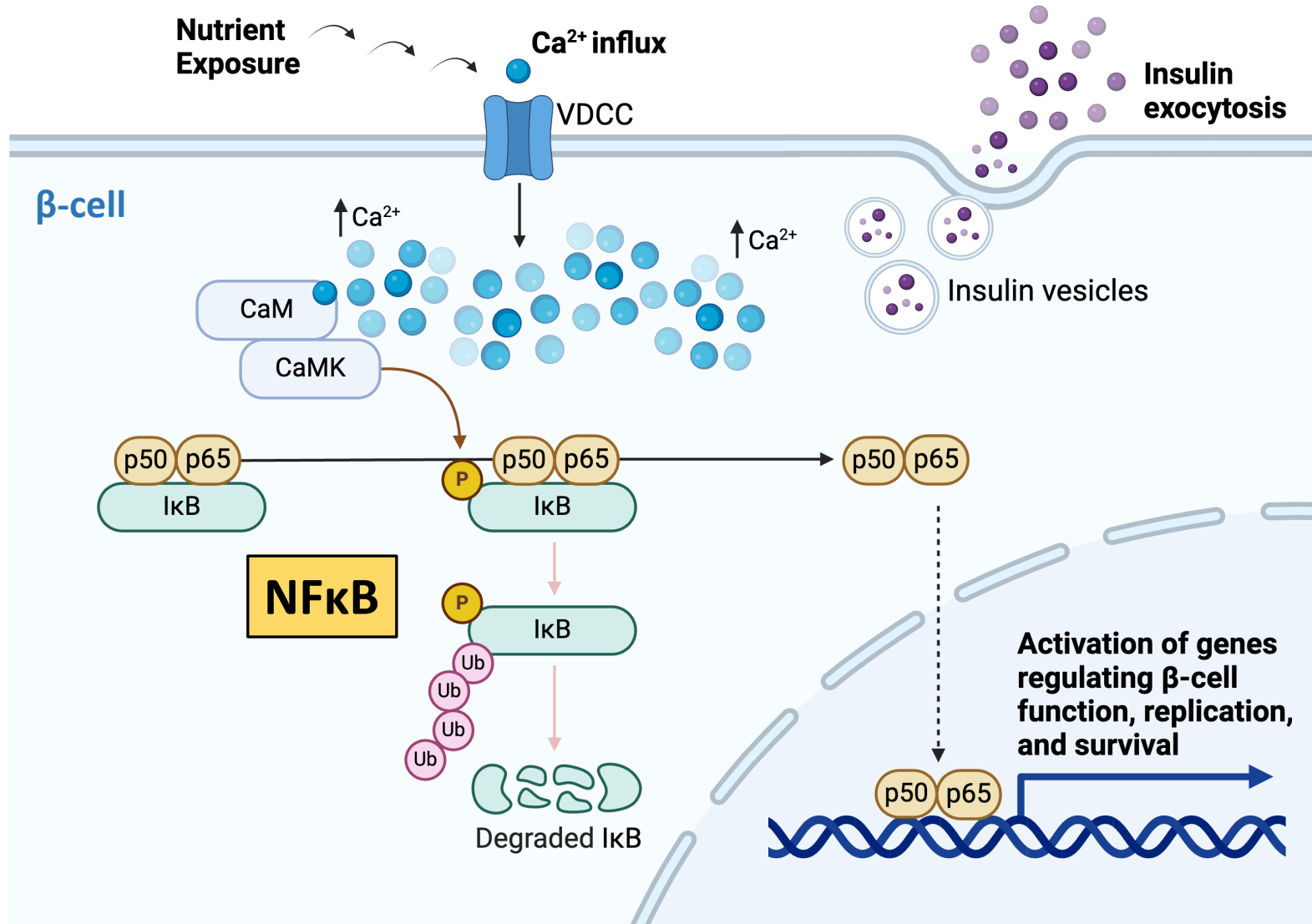
Fetus failing to reach its genetic growth potential



Decreased placental nutrient transfer in FGR



Calcium influx is critical for both insulin secretion and transcriptional changes in the pancreatic β -cell

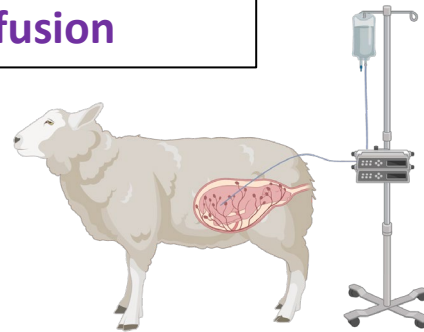


Abbreviations: VDCC, voltage-dependent calcium channel; CaM, calmodulin; CaMK, calcium-calmodulin dependent kinase; I κ B, NF κ B inhibitory protein.

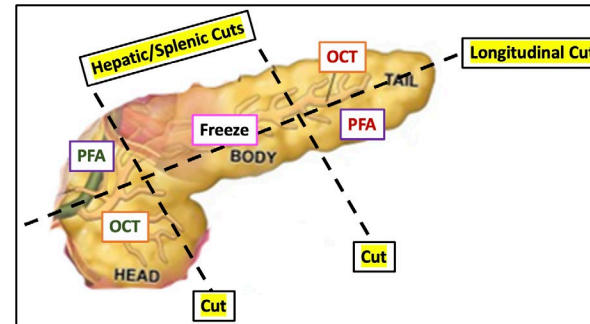
We hypothesize that leucine stimulation will induce NF κ B activation leading to transcriptome changes favoring β -cell function and survival.

Aim 1: Quantify NF κ B signaling in the normally grown fetal sheep pancreas after an *in vivo* leucine infusion

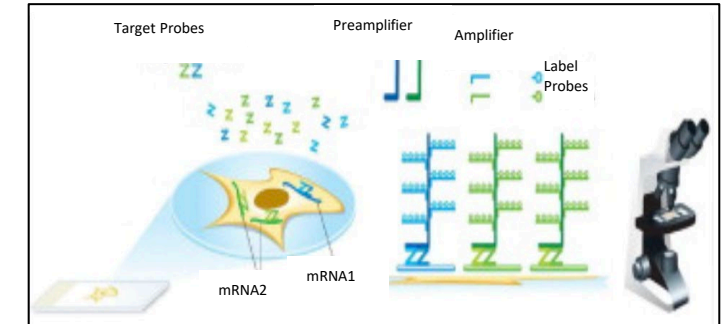
Acute *in vivo* infusion:
vehicle vs leucine



Fetal pancreas
processed for analysis

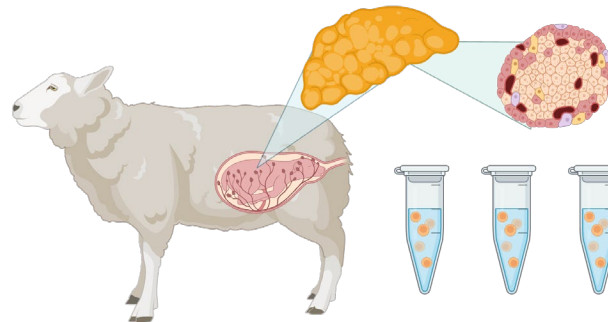


IHC + RNAscope for target
genes within the β -cell

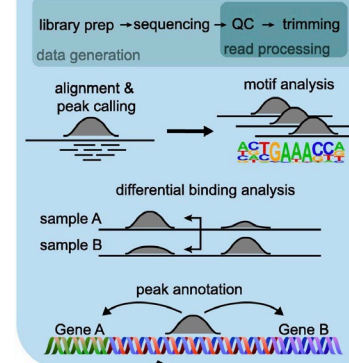


Aim 2: Quantify NF κ B signaling *in vitro* in isolated fetal pancreatic islets in response to nutrient stimulation

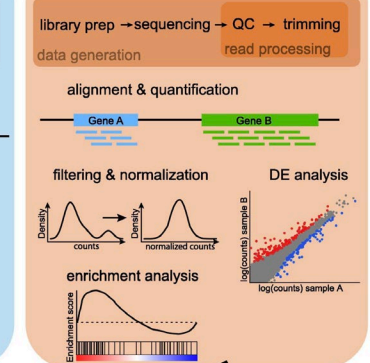
In vitro exposures: vehicle vs leucine



ChIP-seq



RNA-seq



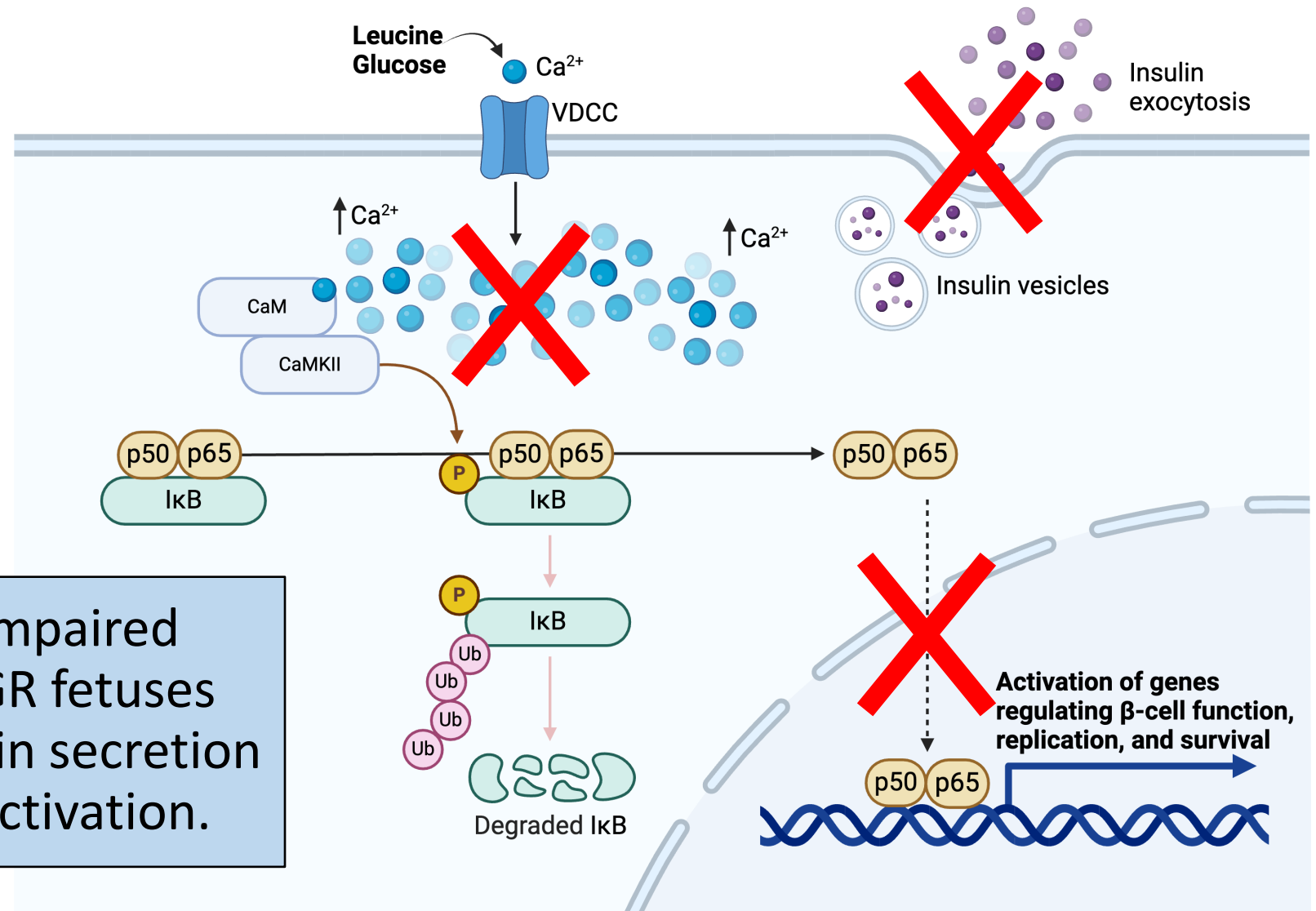
Data integration

CCTSI K12: Do FGR fetal sheep have attenuated β -cell calcium oscillations and therefore reduced NF κ B activity?

FGR

- ↓ Nutrient sensing
- ↓ Oxidative metabolism
- ↓ Insulin secretion
- ↓ β -cell mass & replication

We hypothesize that impaired calcium handling in FGR fetuses leads to reduced insulin secretion and decreased NF κ B activation.



Thank you!

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