Laminin interactions in a 3D reverse thermal gel scaffold promote islet survival under cytokine-mediated stress

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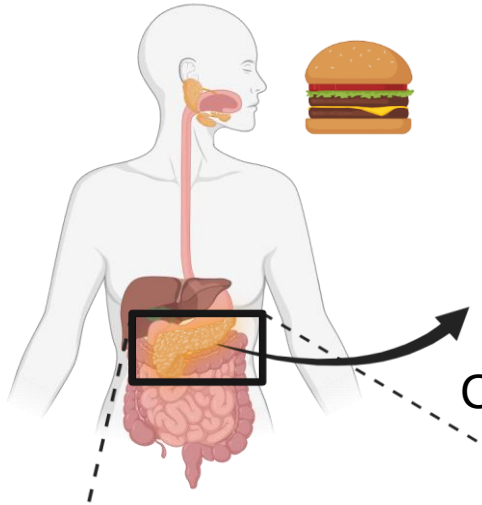
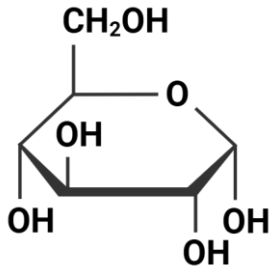
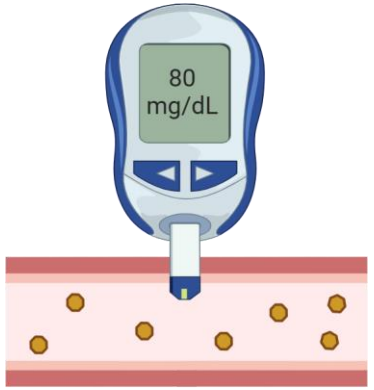
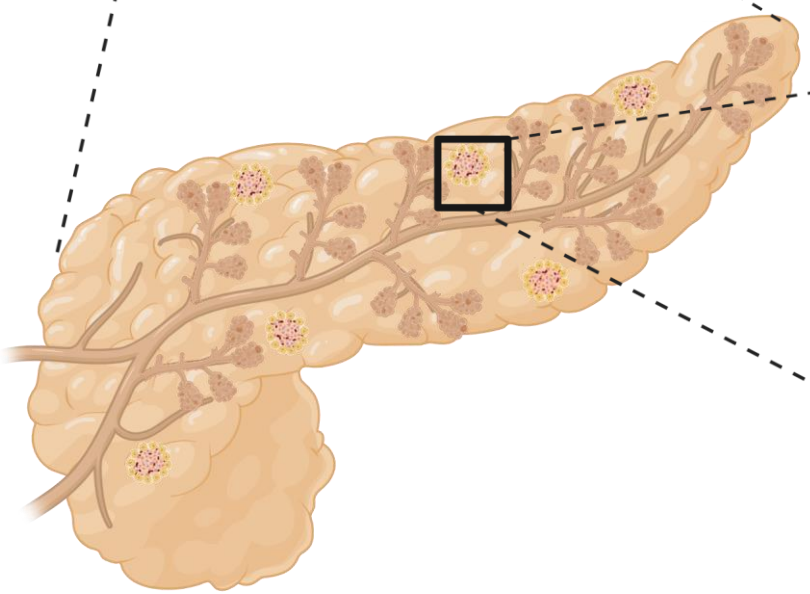


Carbohydrates

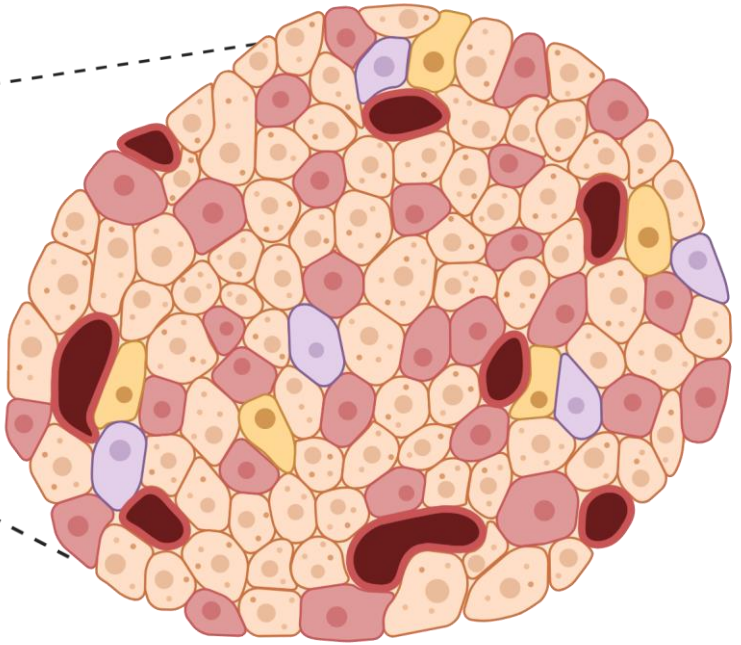


Glucose





Pancreas



Human Islet of Langerhans

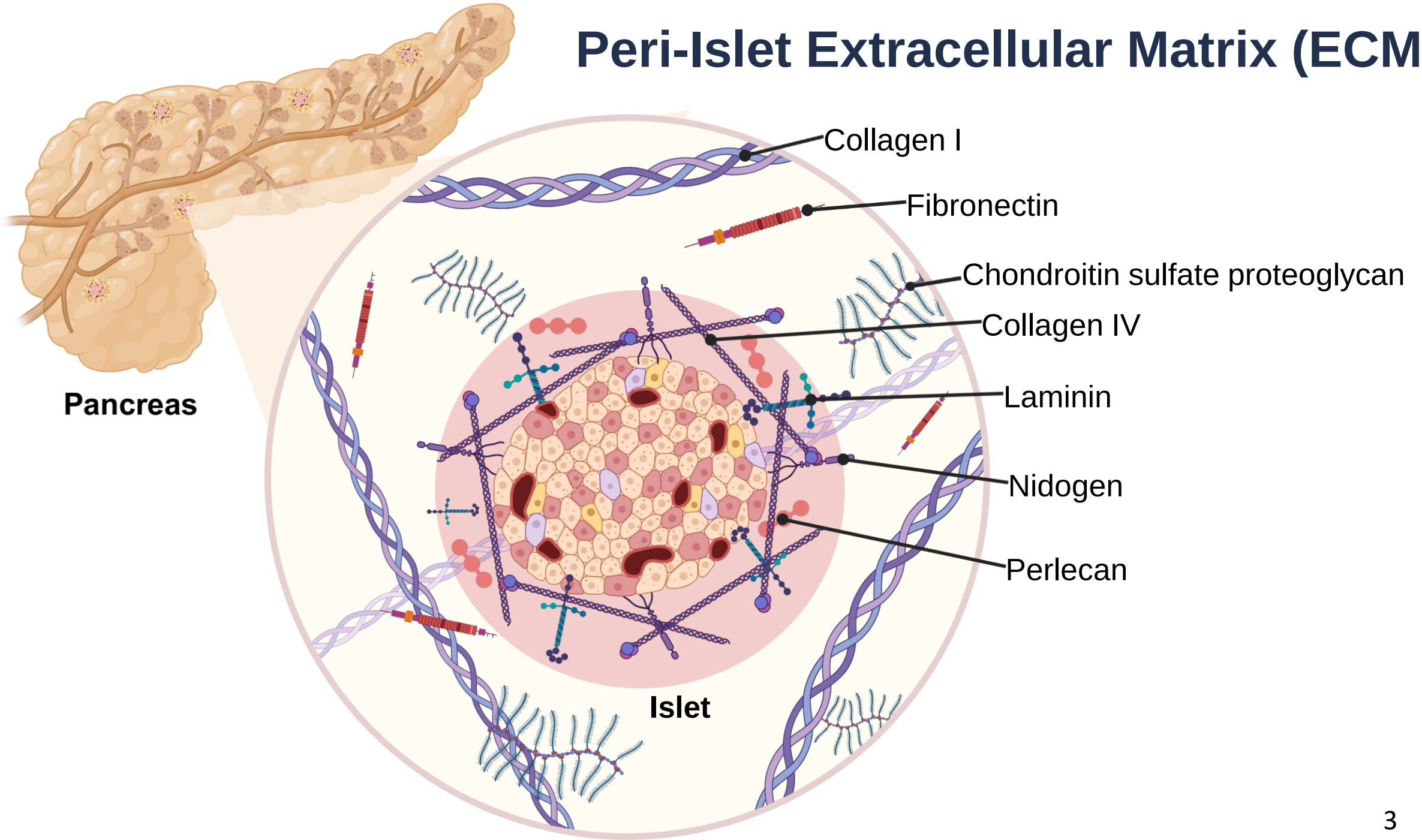
α cell (35%)
(*glucagon*)

β cell (54%)
(***insulin***)

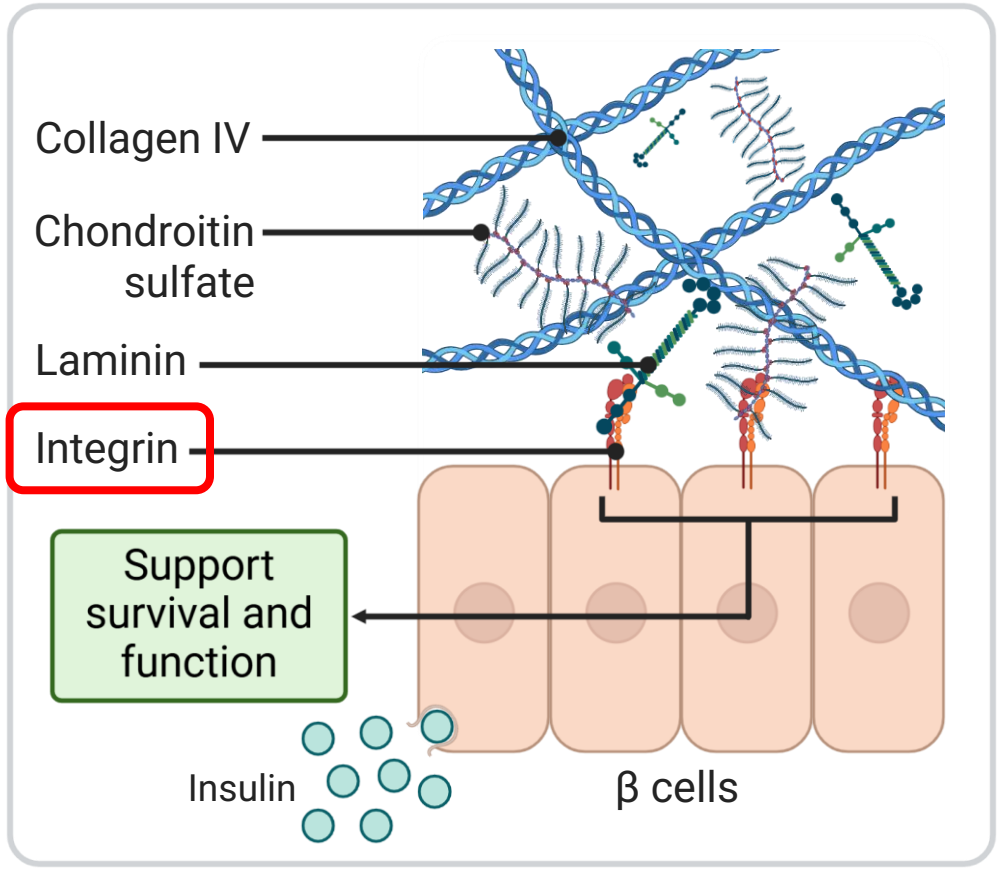
δ cell (<11%)
(*somatostatin*)

PP cell (<5%)
(*pancreatic polypeptide*)

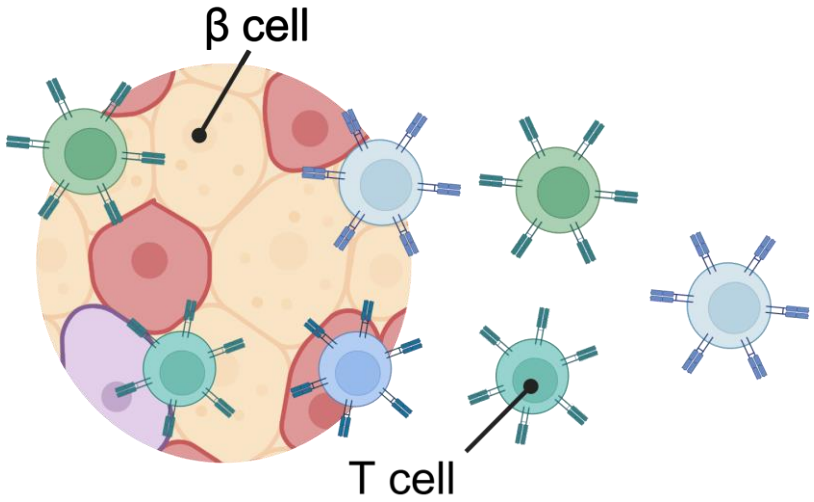
Peri-Islet Extracellular Matrix (ECM)



The ECM Interacts with β Cells via Integrins

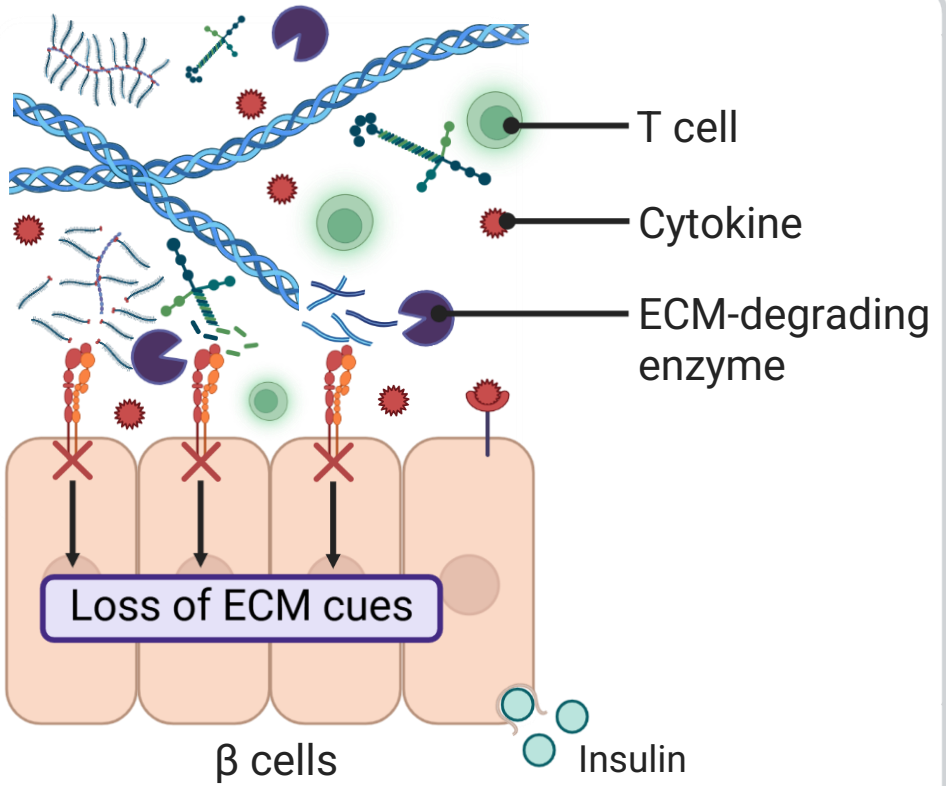


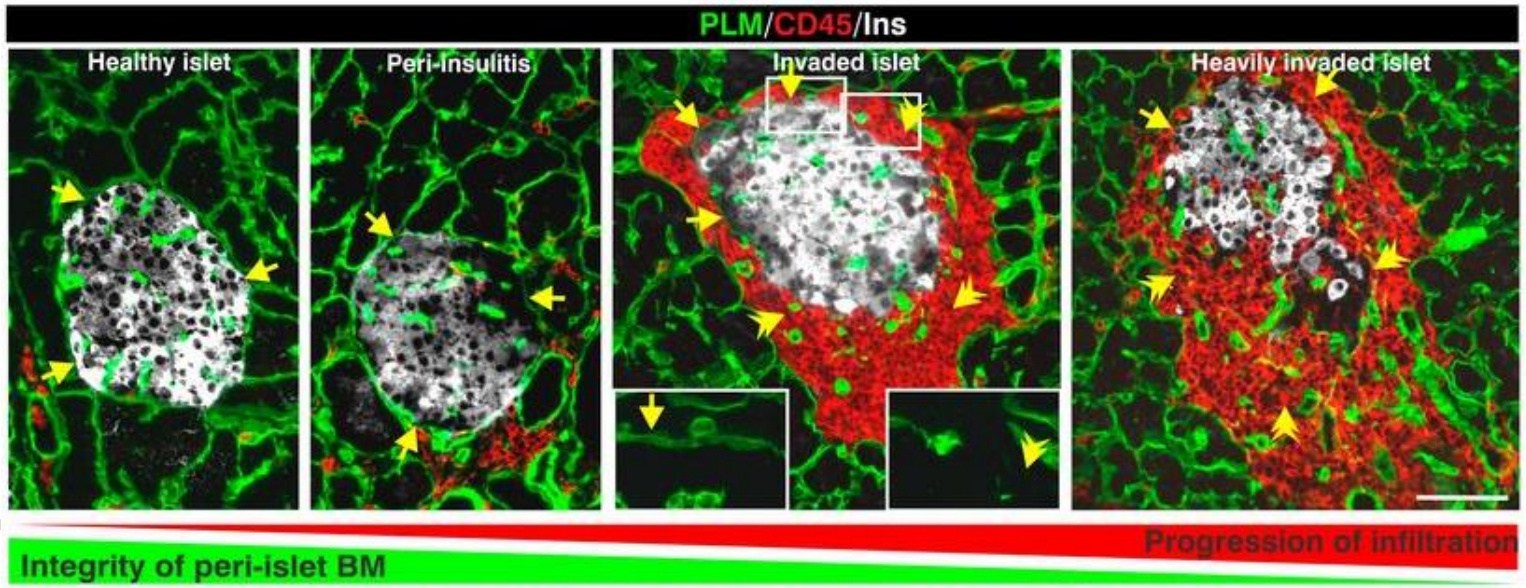
Type 1 diabetes: Immune cells attack and destroy β cells



Bogdani, M. (2014). *Curr. Diab. Rep*.

ECM Degradation in T1D

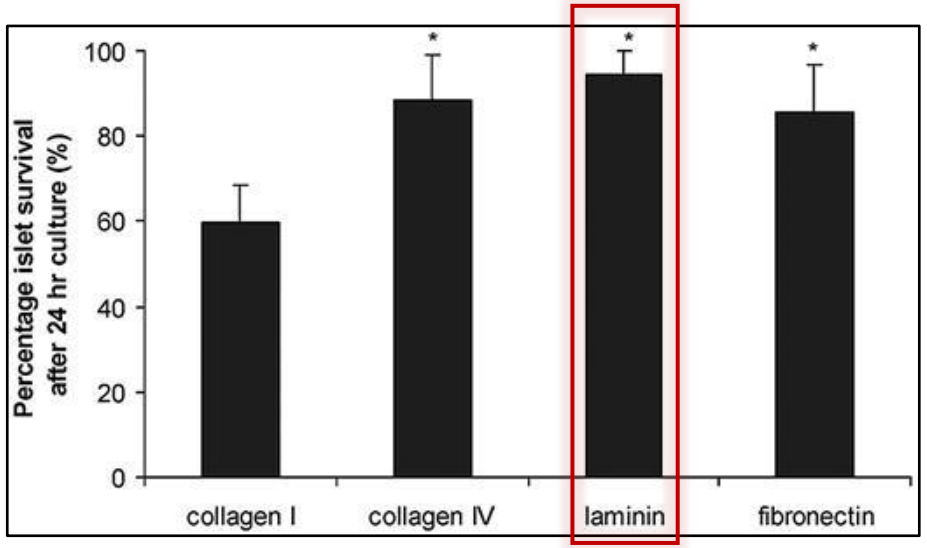


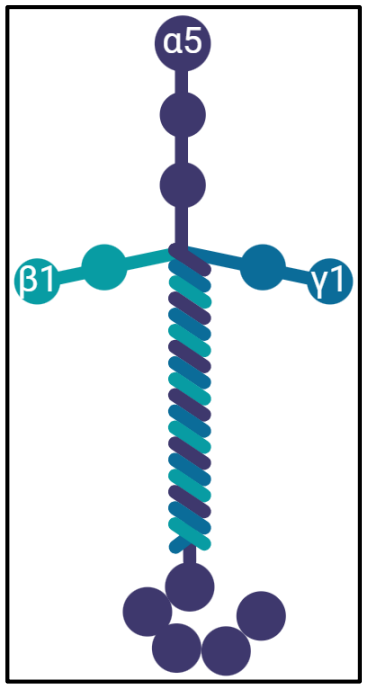


Korpos, É. (2013). *Diabetes.*

Laminin Enhances Islet Survival and Function

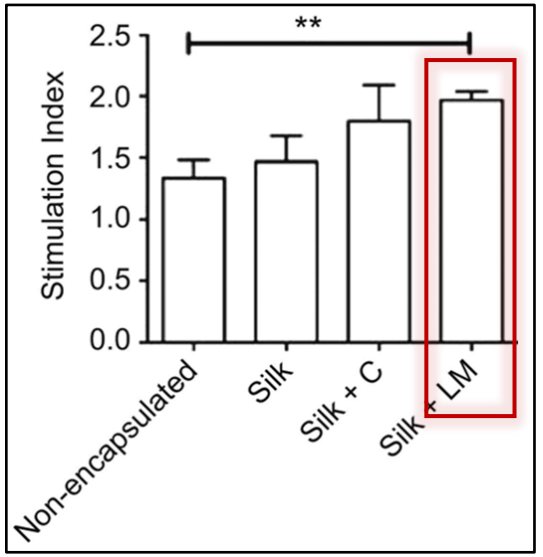
Islet Survival

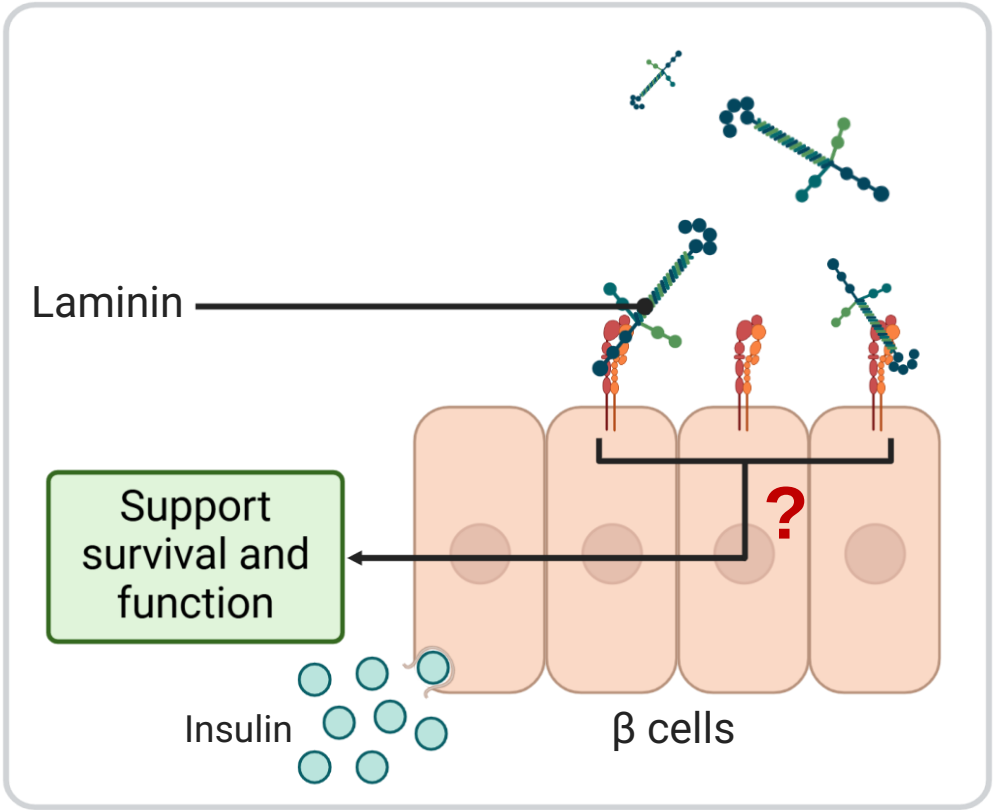




Laminin-511

Islet Function

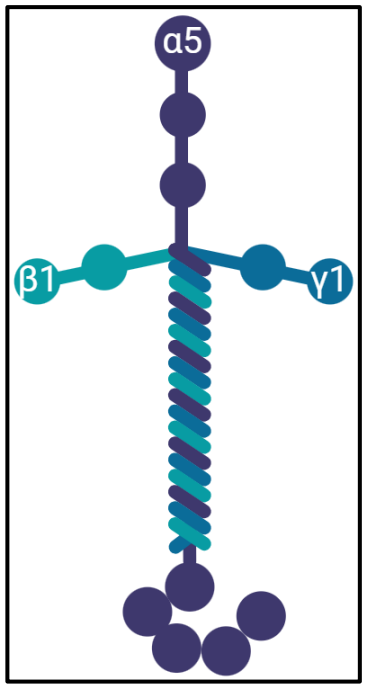




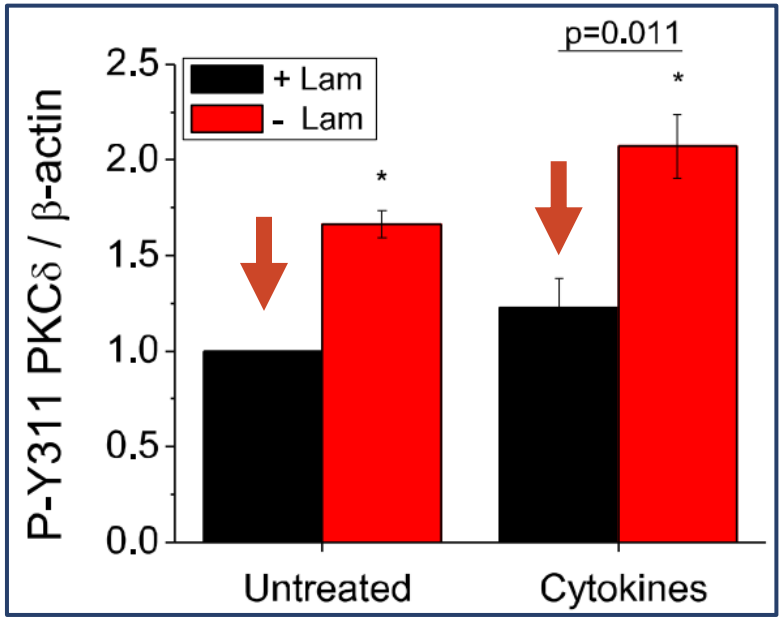
1. Pinkse, G. (2006). *Diabetes*.
2. Davis, N. (2012). *Biomaterials*.

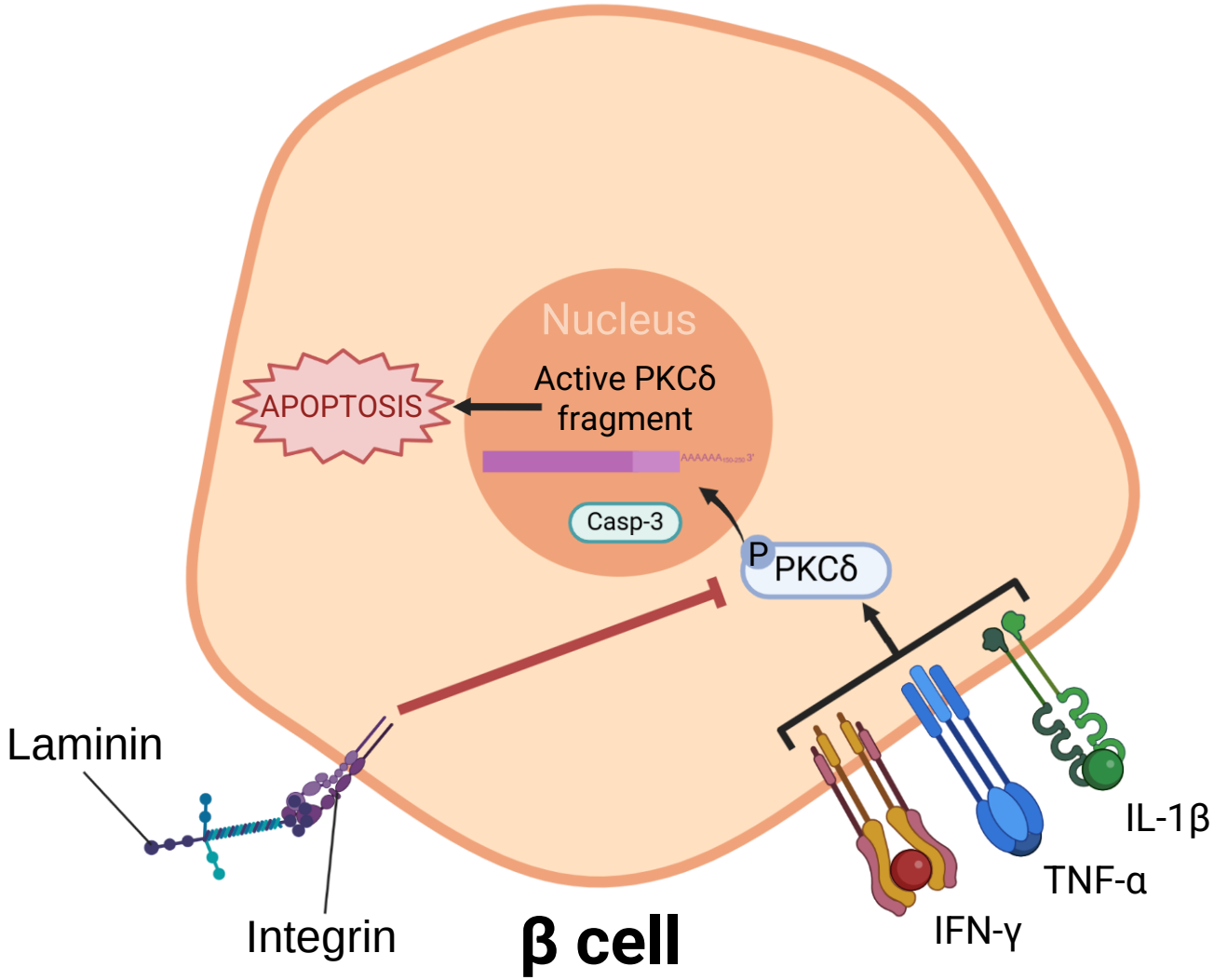
Aim 1: Laminin in the Peri-Islet ECM

PKCδ → Regulates cell death

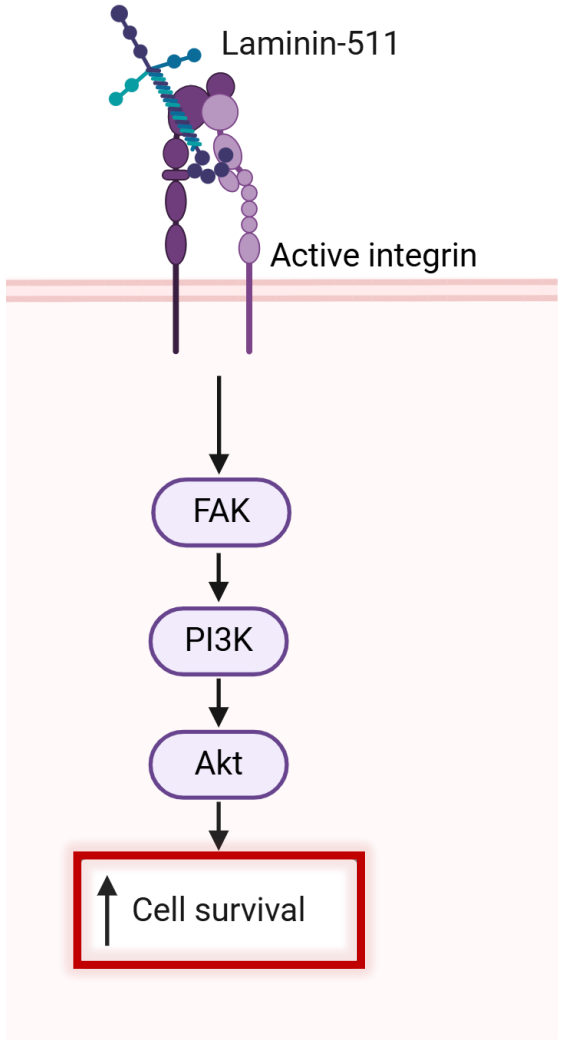


Laminin-511

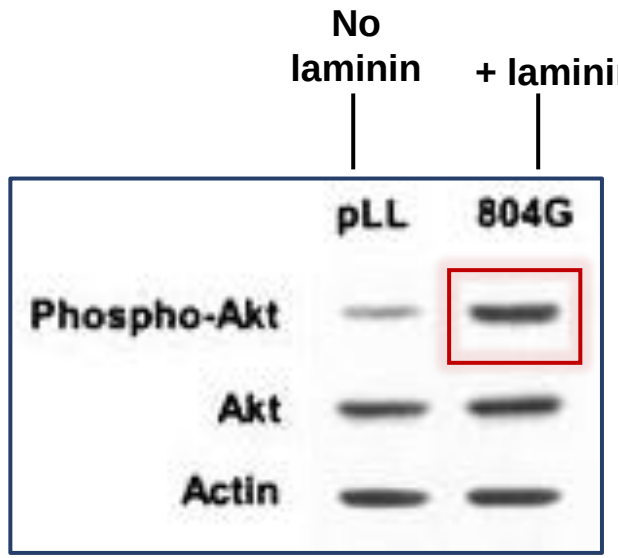




Aim 1: Laminin and the PI3K/Akt Pathway



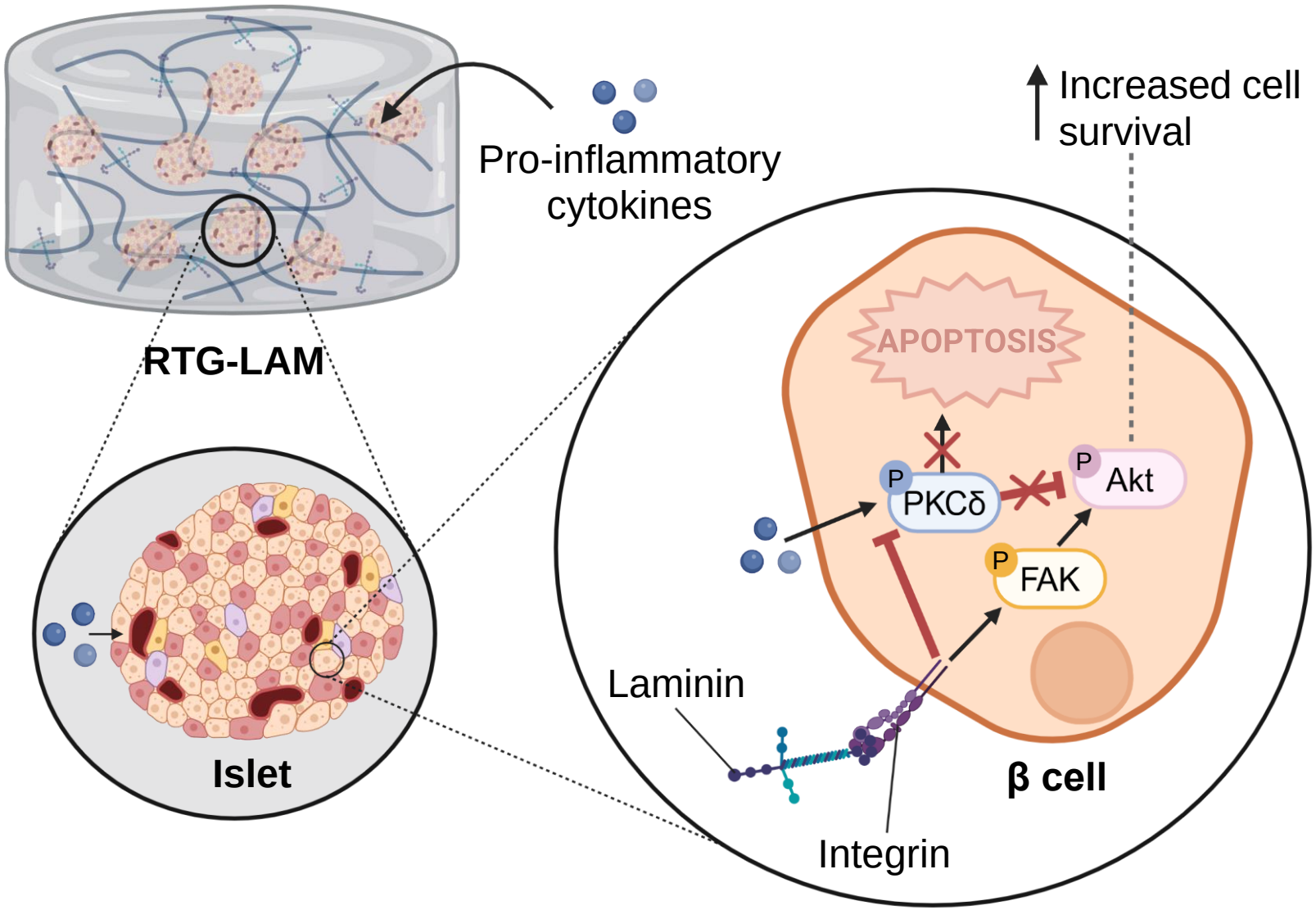
- Akt protects β cells under stress
- Akt activation is increased with laminin



How are these pathways involved in T1D?

Hammar, E. (2004). *Diabetes.*

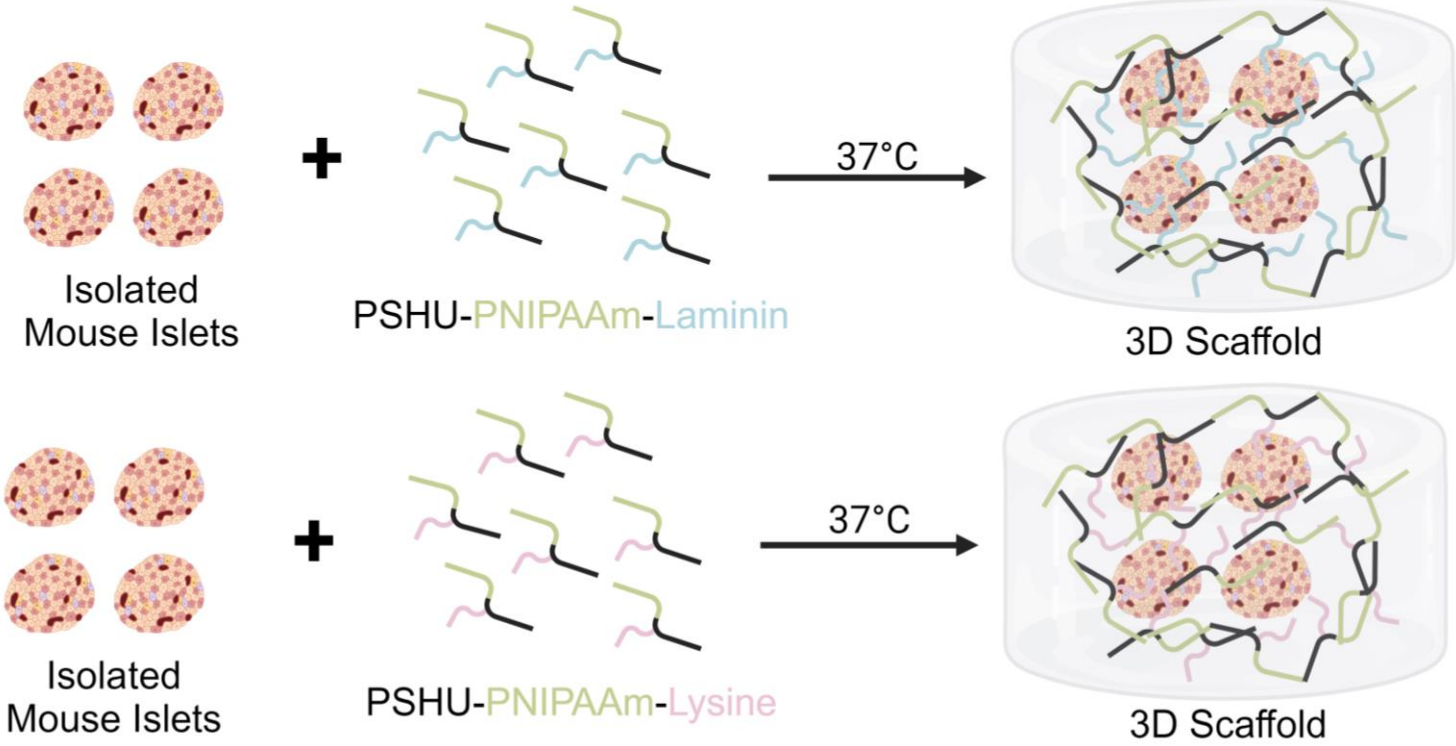
Hypothesis

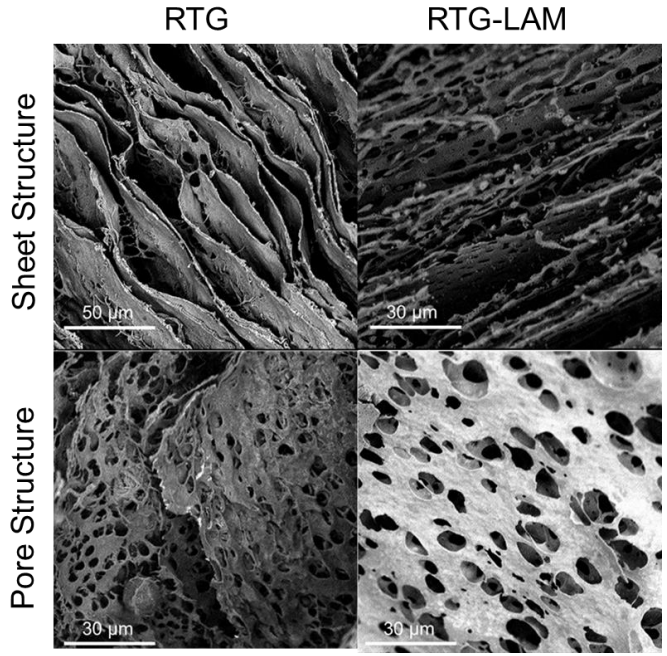


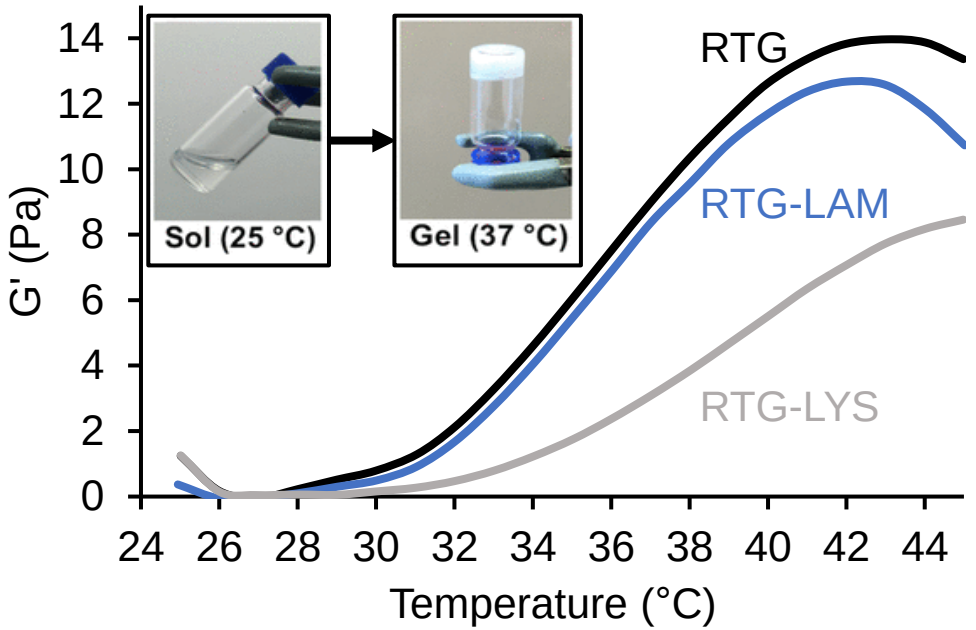
Loss of islet interactions with laminin exacerbates cytokine-mediated β-cell death via activation of PKCδ and impairment of PI3K/Akt signaling.

Aim 1: Laminin-Functionalized Biomimetic Scaffold

Poly(serinol hexamethylene urea) (**PSHU**) is conjugated to poly(*N*-isopropylacrylamide) (**PNIPAAm**) to create a reverse thermal gel (**RTG**)

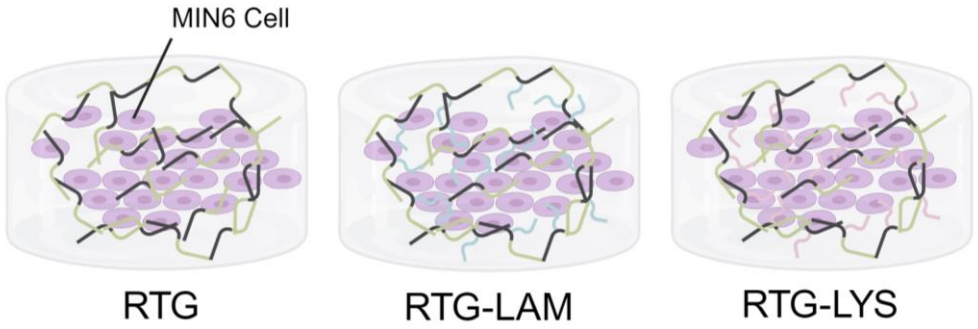




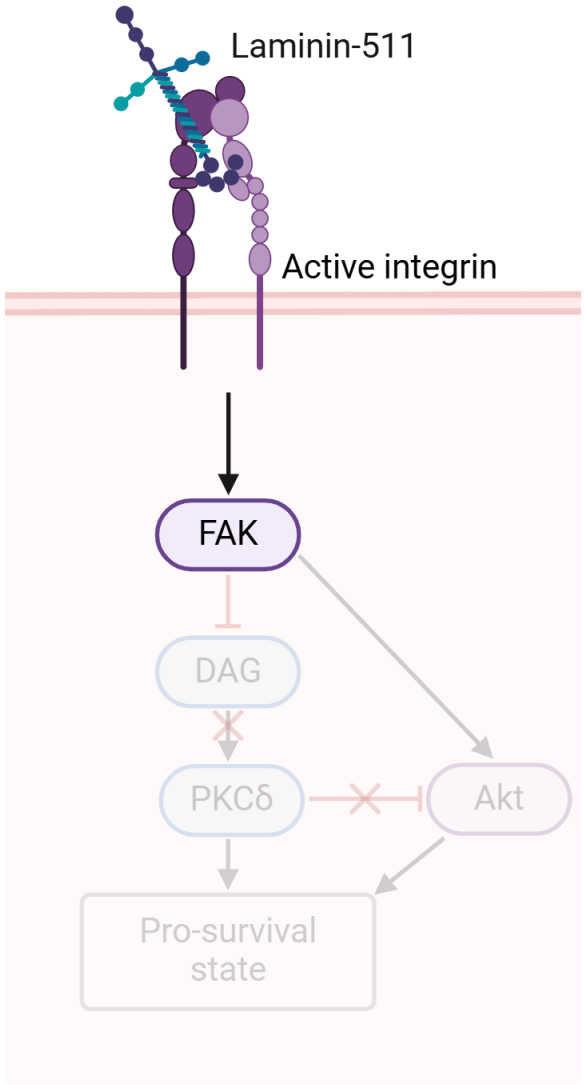


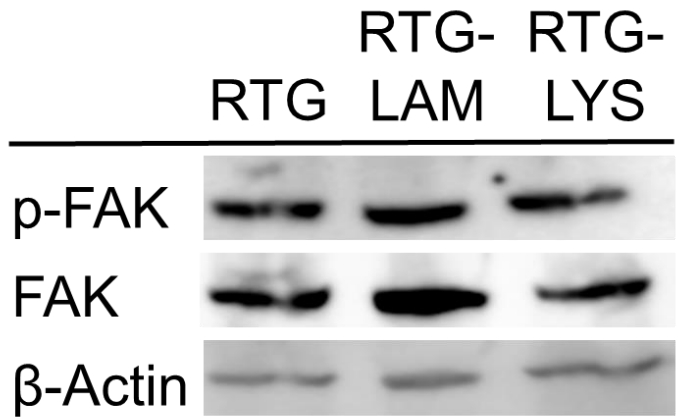
Aim 1: FAK Activation by Integrin Interactions

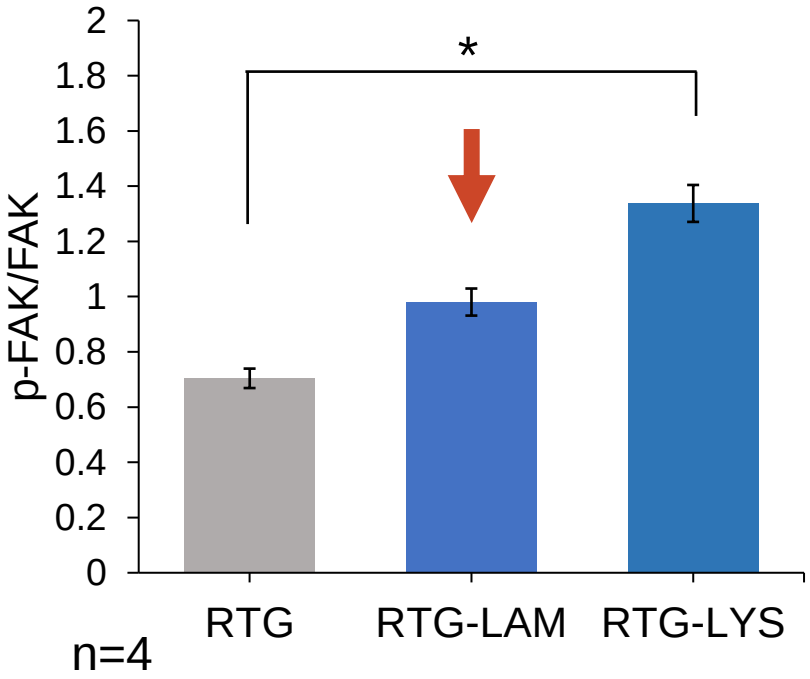
- FAK is activated upon ECM interactions with integrins



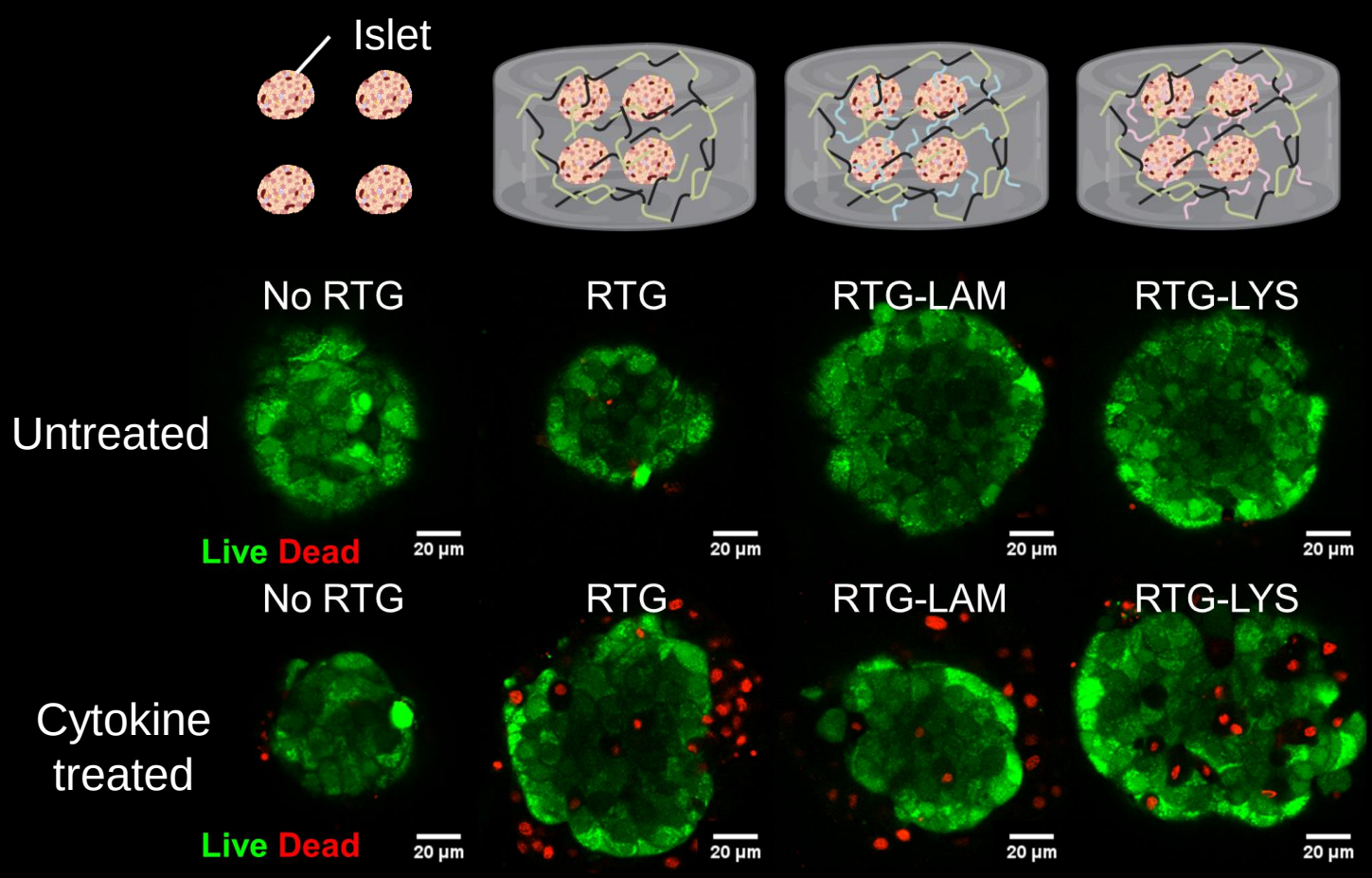
Laminin binding activates FAK to initiate the signaling pathway



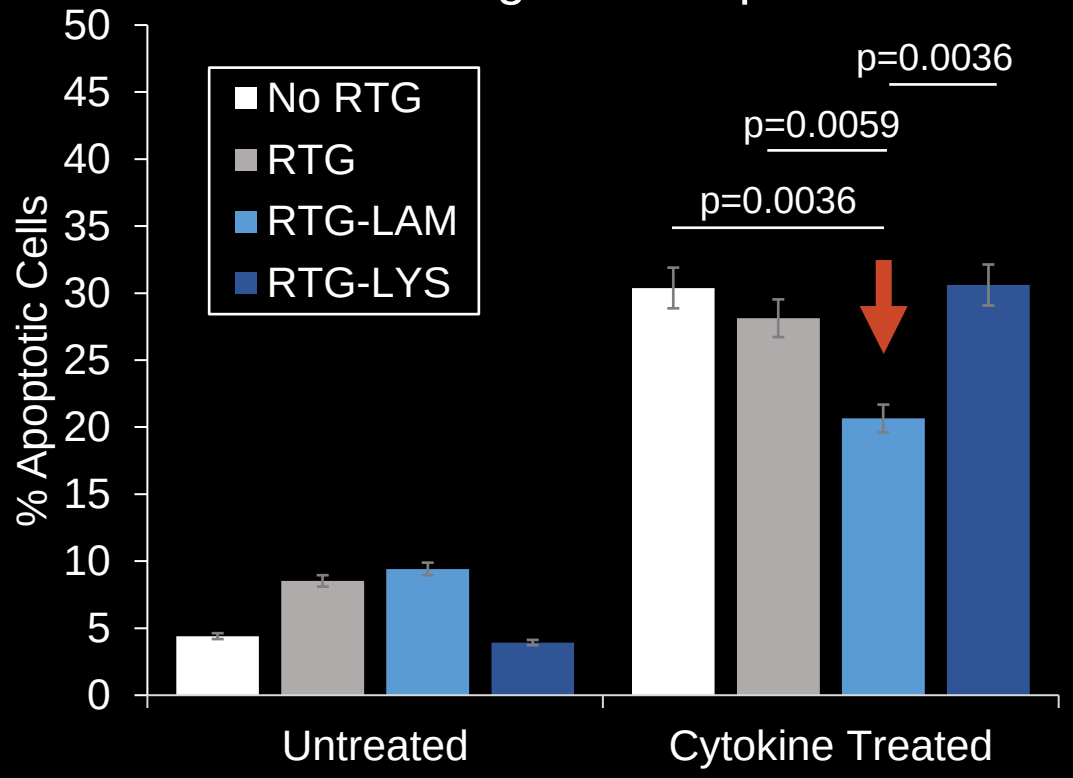




Aim 1: Laminin Promotes Islet Survival Under Stress



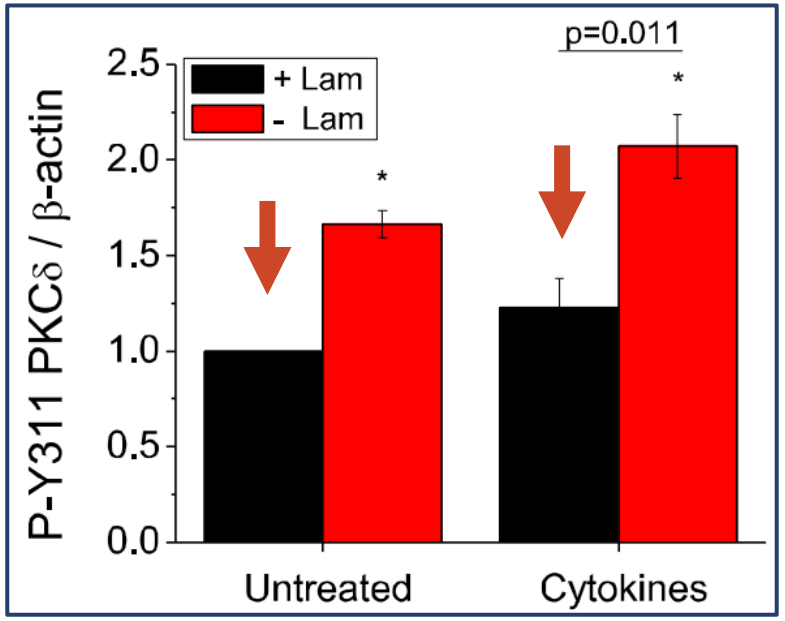
Pro-Inflammatory Cytokine Cocktail:
10 ng/mL TNF-α
5 ng/mL IL-1β
100 ng/mL INF-γ



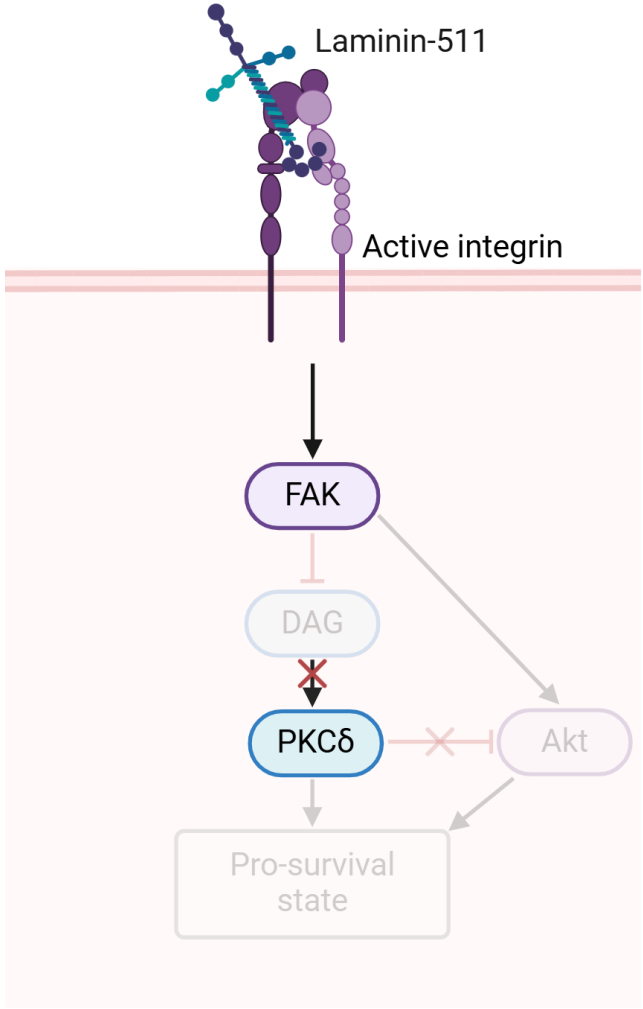
n=3

Laminin interactions protect against cytokine-mediated cell death

Aim 1: Impact of Laminin on PKCδ Activation

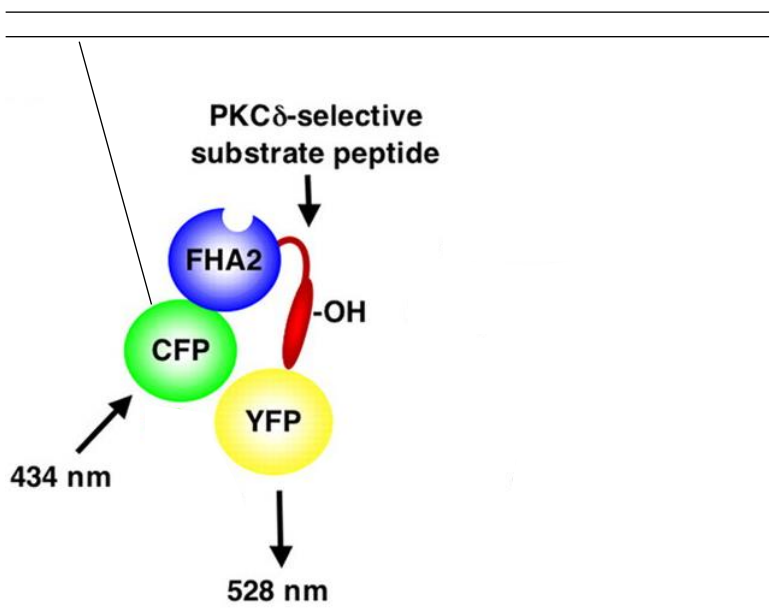


- Laminin suppresses PKCδ activity

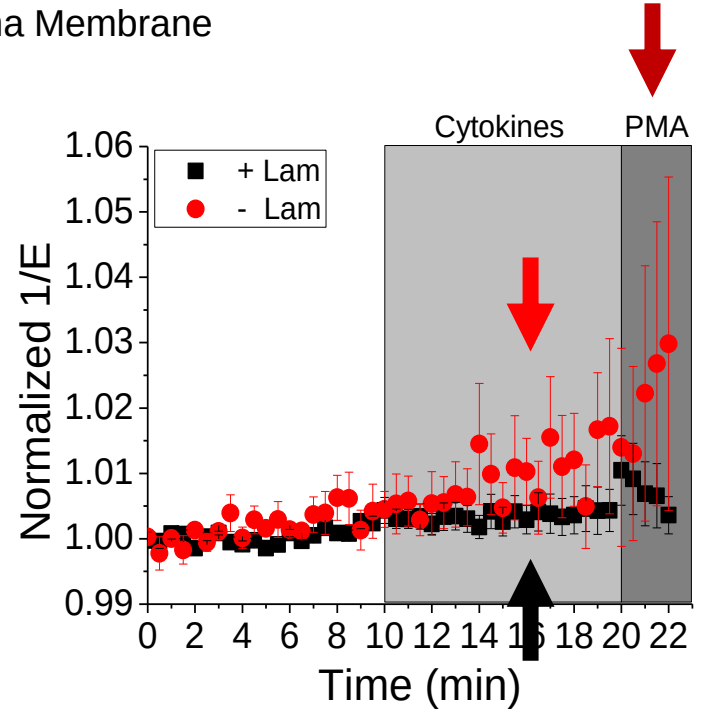


Aim 1: Laminin Downregulates PKCδ Activity

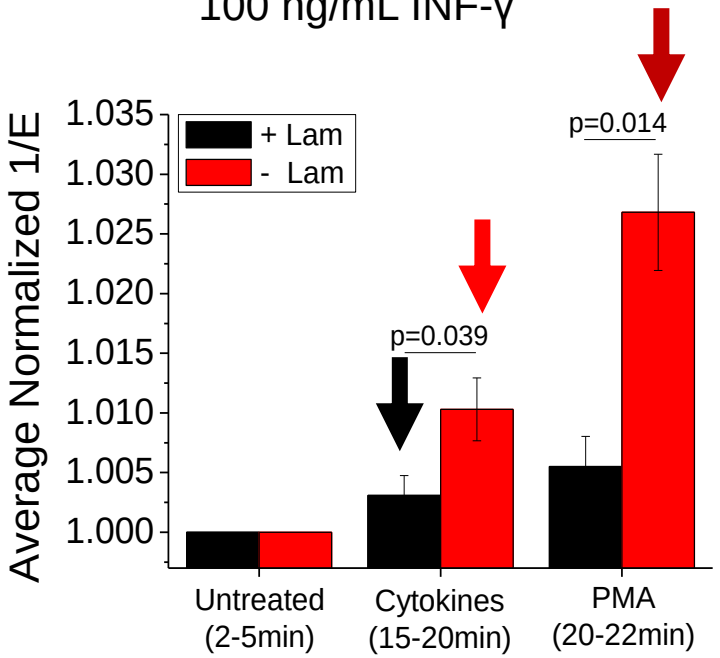
Forster resonance energy transfer (FRET)



Membrane-tagged PKCδ FRET sensor



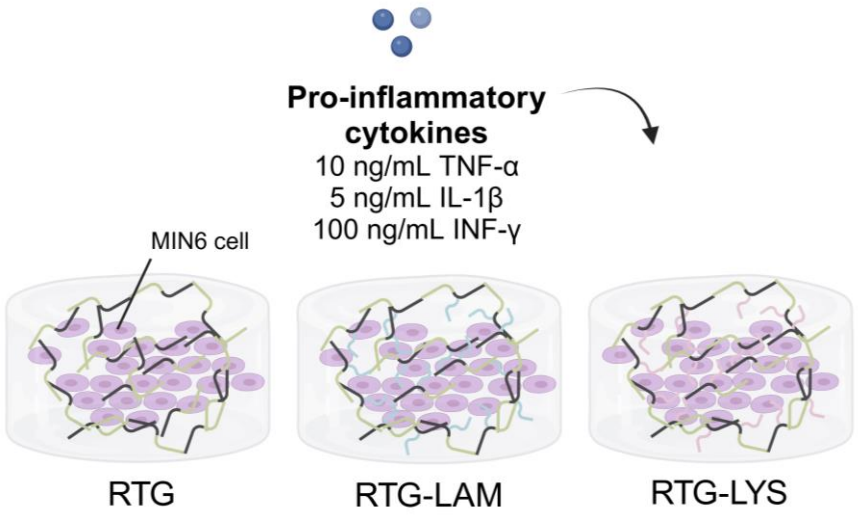
Pro-Inflammatory Cytokine Cocktail:
10 ng/mL TNF-α
5 ng/mL IL-1β
100 ng/mL INF-γ



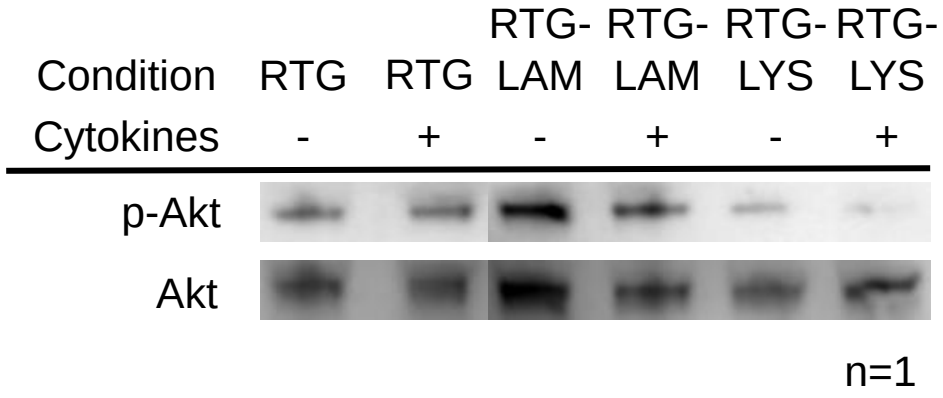
Loss of laminin increases PKCδ activity at the cell membrane and amplifies the cell's response to cytokines.

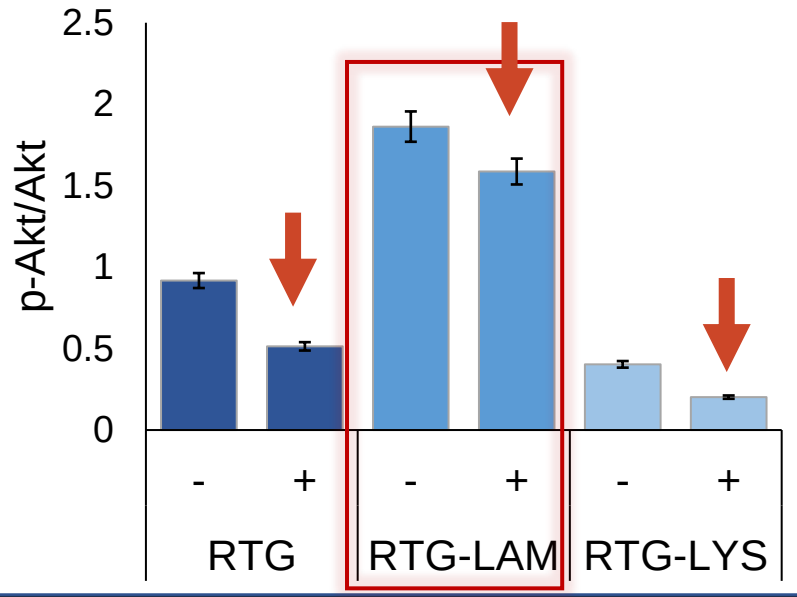
Kajimoto, T. (2010). *Biol. Chem.*

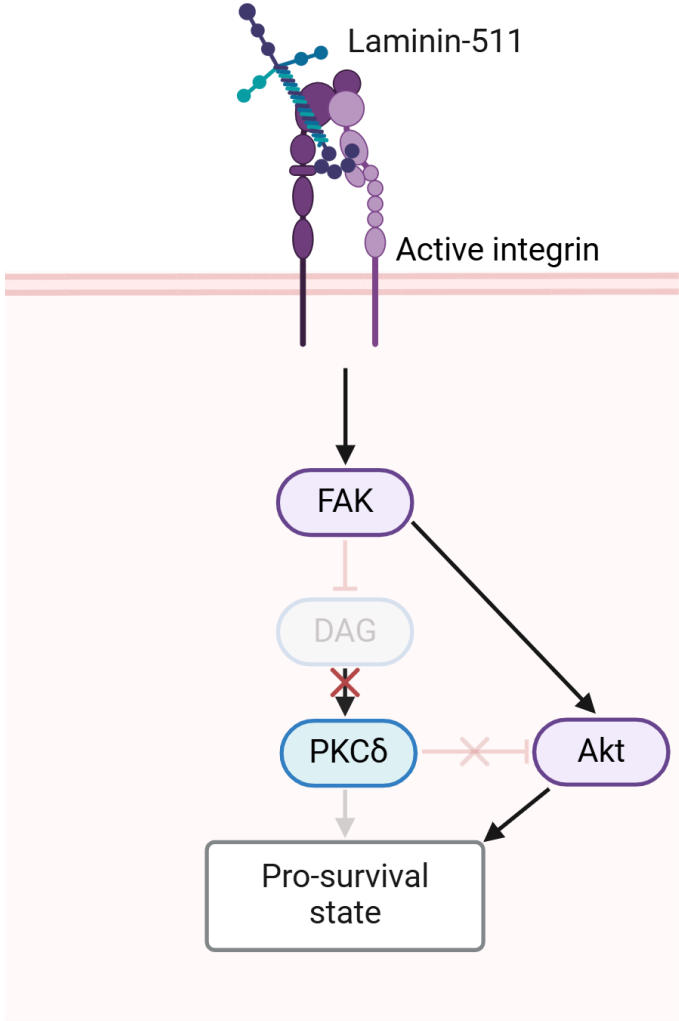
Aim 1: Laminin Activates PI3K/Akt Pathway



Laminin activates the PI3K/Akt pathway to protect against cytokine-mediated death

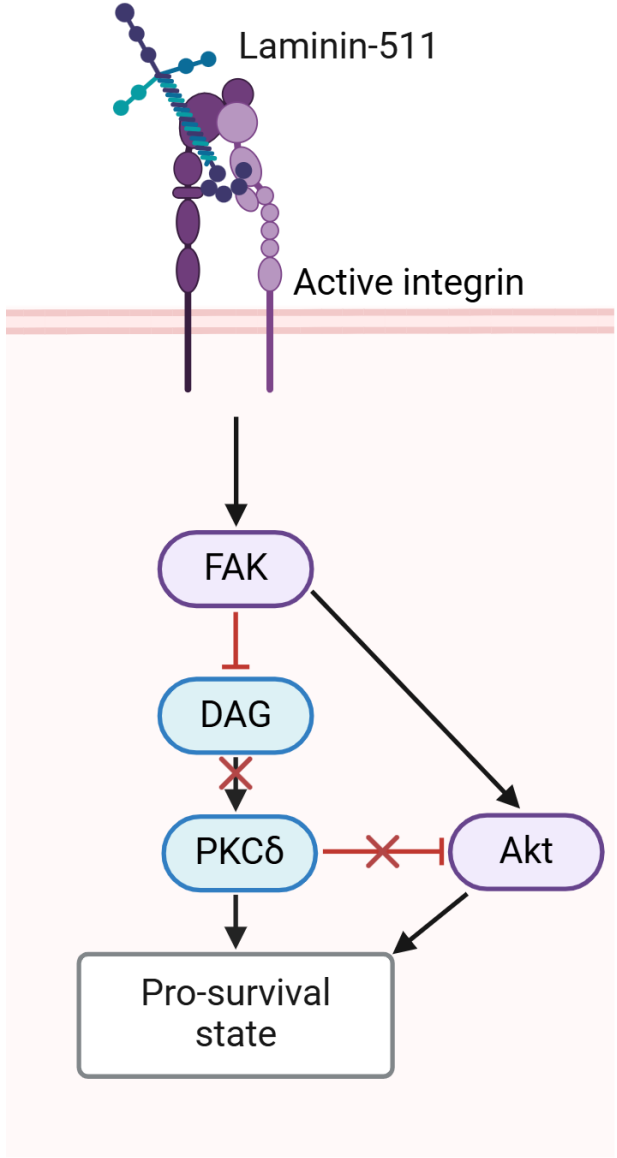






Conclusions & Future Work

- Loss of important ECM molecules like laminin during T1D
- Future work involves exploring these mechanisms
- Potential therapies at each stage of disease
  - Restore islet microenvironment
  - Protect β cells & preserve function



Acknowledgements

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Dr. Nikki Farnsworth – Advisor

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Chelsea Garcia
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Sara Núñez
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MINES QUANTITATIVE BIOSCIENCES & ENGINEERING

University of Colorado Anschutz Medical Campus

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Questions

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