Trophoblast-mediated tolerance in Type 1 Diabetes Autoimmunity

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Motivation

During pregnancy, the placenta prevents the maternal immune system from rejecting the semi-allogeneic fetus, and gestation has been shown to delay T1D (Type 1 Diabetes) onset in NOD (Non Obese Diabetic) mice [1]. This suggests that placenta-derived factors may modulate islet autoimmunity and could be used as a prophylactic in at-risk individuals.

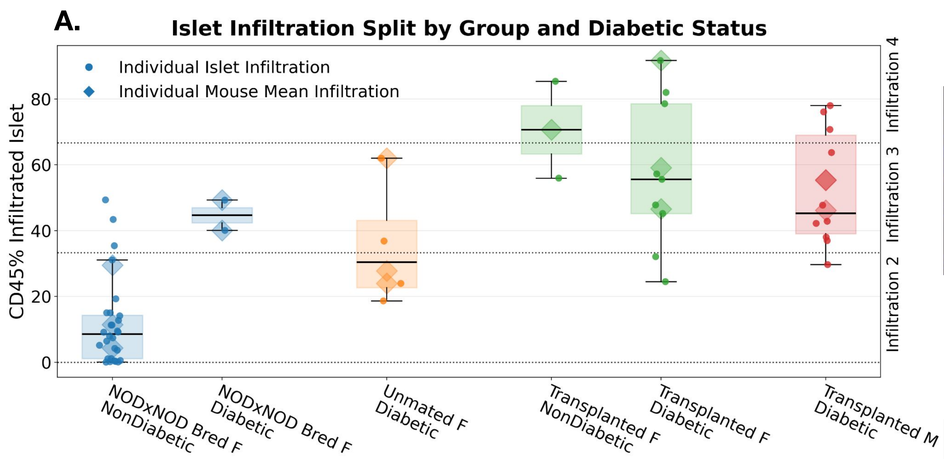
Hypothesis: Subcutaneously transplanted JAR cells (human placental trophoblast choriocarcinoma line) encapsulated in a hydrogel spiral will secrete immunomodulatory factors that delay T1D autoimmunity in NOD mice, translating pregnancy-mediated tolerance into a prophylactic.

Objectives

1. Confirm gestation delays T1D in female NOD mice.
2. Compare pancreatic histology across cohorts to quantify immune infiltration.
3. Evaluate whether transplanted JAR cells delay T1D in female and male NOD mice.

Results

Figure 1.



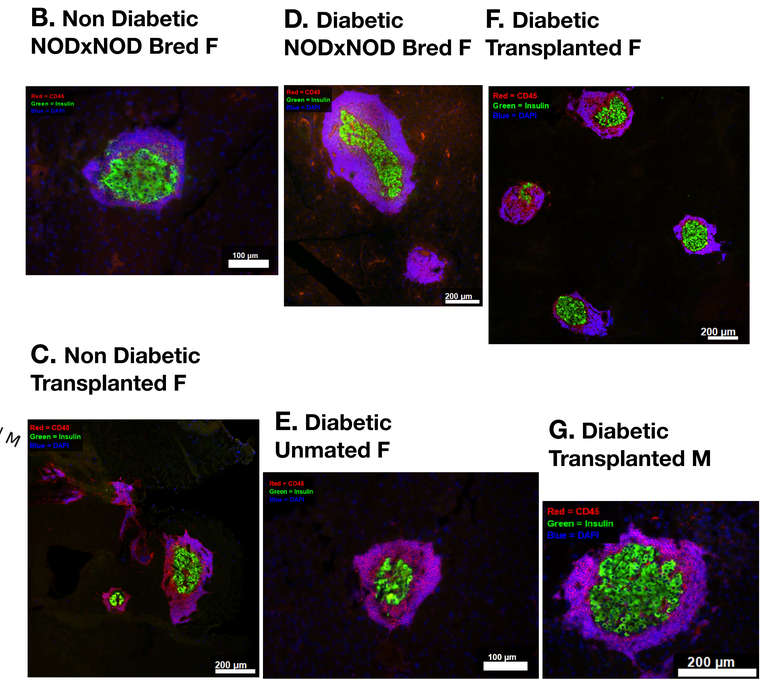


Fig 1. [A] Quantification of CD45 infiltration by cohort, split by diabetic status. Left y-axis shows percent CD45 area per islet; right y-axis shows the corresponding insulitis score (2–4). Dots represent individual islets; diamonds represent per-mouse means. **[B–G]** Representative islets at 20× magnification stained for insulin (green), CD45 (red), and DAPI (blue).

Conclusions & Future Work

Bred non-diabetic NOD females showed the lowest CD45 infiltration of any cohort, consistent with a pregnancy-mediated tolerogenic effect. Transplanted cohorts scored high, likely reflecting small sample sizes and the xenogeneic mismatch between human JAR cells and non-humanized NOD mice; in humanized mice, the transplants may exert a stronger tolerogenic effect. Glucagon co-staining would also have sharpened the readout, allowing detection of β-cell–depleted islets that were missed.

Future Work: Co-stain with glucagon to enable peri-insulitis scoring of 1 and capture insulin-negative islets; incorporate islet size into scoring, since large and small islets with equal percent infiltration are currently weighted the same; expand cohort sizes; and repeat in humanized NOD mice for a more allogeneic effect from the JAR cells.

Method

Figure 2. Macro Quantification and Validation

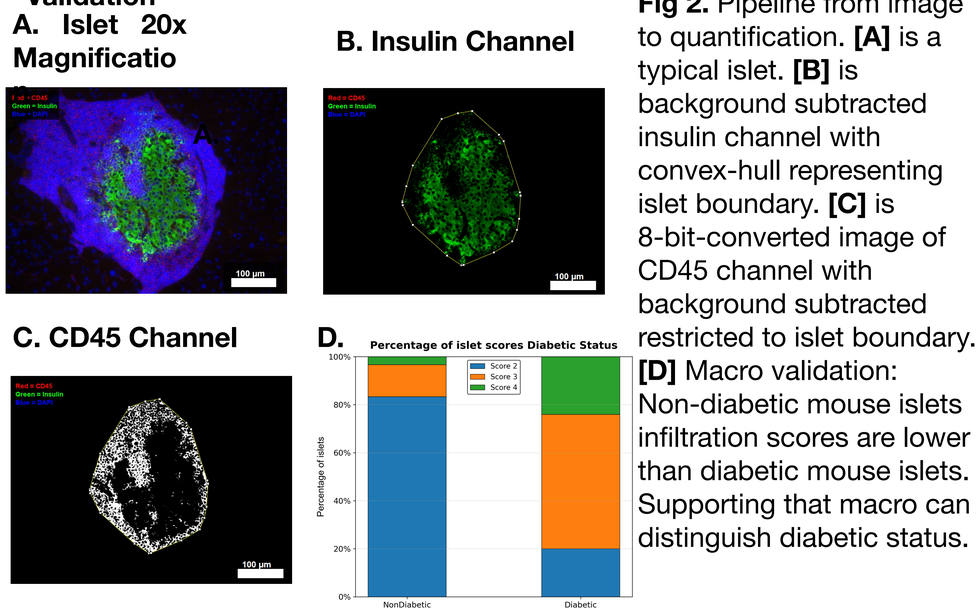


Fig 2. Pipeline from image to quantification. **[A]** is a typical islet. **[B]** is background subtracted insulin channel with convex-hull representing islet boundary. **[C]** is 8-bit-converted image of CD45 channel with background subtracted restricted to islet boundary. **[D]** Macro validation: Non-diabetic mouse islets infiltration scores are lower than diabetic mouse islets. Supporting that macro can distinguish diabetic status.

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References

[1] A. J. Dwyer et al., "Enhanced CD4+ and CD8+ T cell infiltrate within convex hull defined pancreatic islet borders as autoimmune diabetes progresses," Sci Rep, vol. 11, no. 1, p. 17142, Aug. 2021, doi: 10.1038/s41598-021-96327-2.

[2] K. Adler, S. Krause, Y. F. Fuchs, K. Foertsch, A.-G. Ziegler, and E. Bonifacio, "The effect of gestation and fetal mismatching on the development of autoimmune diabetes in non-obese diabetic mice," Clin Exp Immunol, vol. 168, no. 3, pp. 274–278, Jun. 2012, doi: 10.1111/j.1365-2249.2012.04579.x.