

DECODING ACUTE REJECTION-INDUCED ISLET INJURY IN PANCREAS TRANSPLANTATION

Tim Swaab^{1,2}, Maria Ramirez-Bajo^{2,3}, Alejandro Álvaro-Meca⁴, Charlotte Franken², Jordi Rovira^{2,3}, Elisenda Bañón-Maneus^{2,3}, Enrique Montagud-Marrahi^{2,3,5}, Ivan Archilla⁶, Mangeles Garcia-Criado⁷, Joana Ferrer-Fàbrega⁸, Fritz Diekmann^{2,3,5}, Robert Pol¹, Pedro Ventura-Aguir^{2,3,5}

1. University Medical Center Groningen, Department of Surgery, Division of Transplantation Surgery, Groningen, the Netherlands, 2. Fundació de Recerca Clínic Barcelona- Institut d'Investigacions Biomèdiques August Pi I Sunyer (FRCB- IDIBAPS), Laboratori Experimental de Nefrologia i Trasplantament (LENIT), Barcelona, Spain, 3. Redes de Investigación Cooperativa Orientadas a Resultados en Salud (RICORS), Madrid, Spain, 4. Rey Juan Carlos University, Department of Preventive Medicine and Public Health, Madrid, Spain, 5. Hospital Clínic Barcelona, Department of Nephrology and Kidney Transplantation, Barcelona, Spain, 6. Hospital Clínic Barcelona, Department of Pathology, Center for Biomedical Diagnosis, Barcelona, Spain, 7. Hospital Clínic Barcelona, Department of Radiology, Center for Biomedical Imaging, Barcelona, Spain, 8. Hospital Clínic Barcelona, Department of Hepatobiliary Surgery, Barcelona, Spain

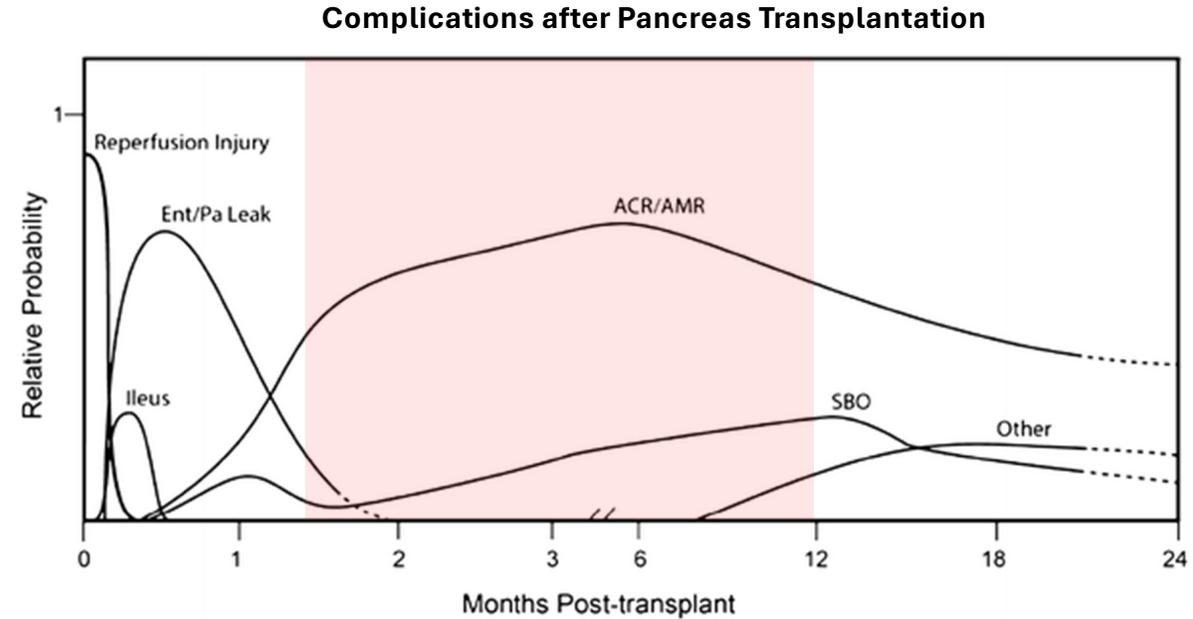


Rejection in Pancreas Transplantation

Acute cellular rejection (ACR) = Major complication following pancreas transplantation (~ 1.5 – 12 months).

Incidence: **10 – 15%**

Prognostic Impact



Rejection in Pancreas Transplantation

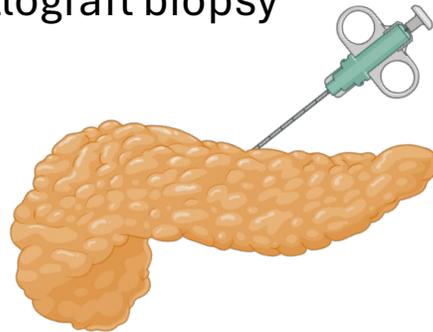
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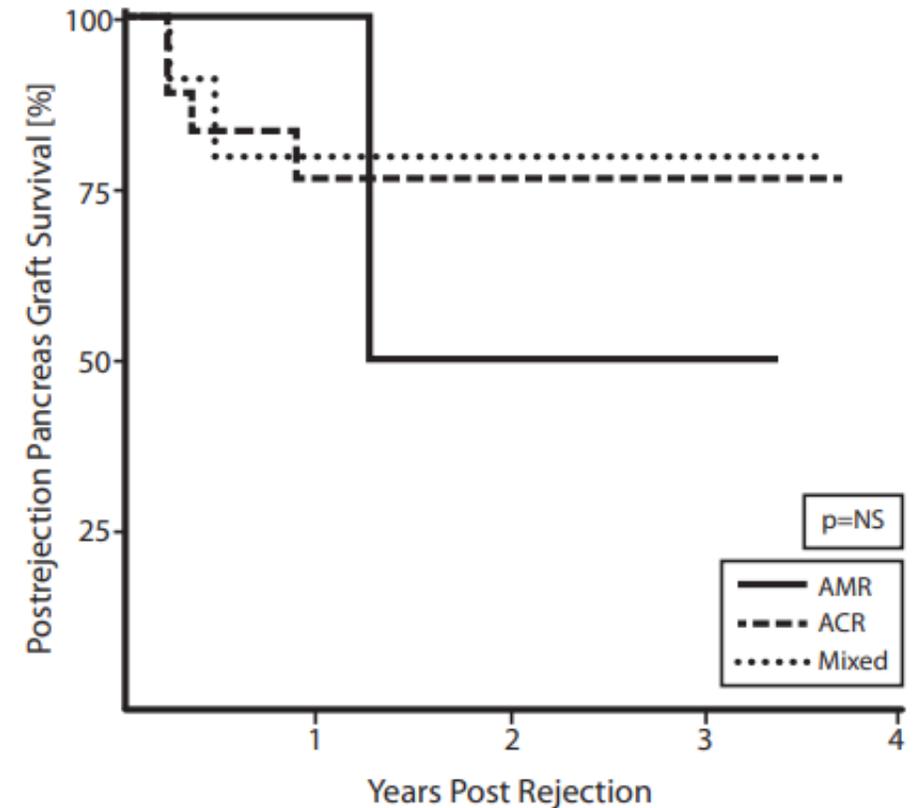
Prognostic Impact

- Diminished long term graft function and survival
- Leading cause of graft loss/failure >3 months
- Up to 25% of grafts lost <1 year of a rejection episode

Diagnostic **gold** standard = Allograft biopsy



Pancreas Allograft Survival After AMR, ACR, or Mixed Rejection

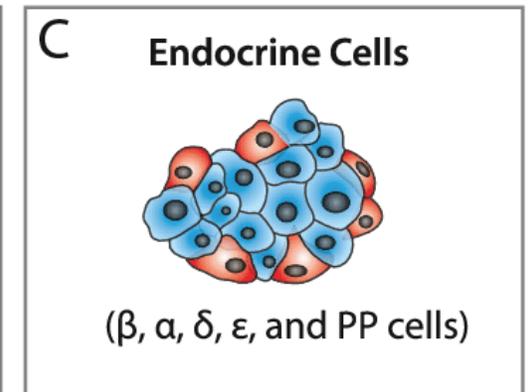
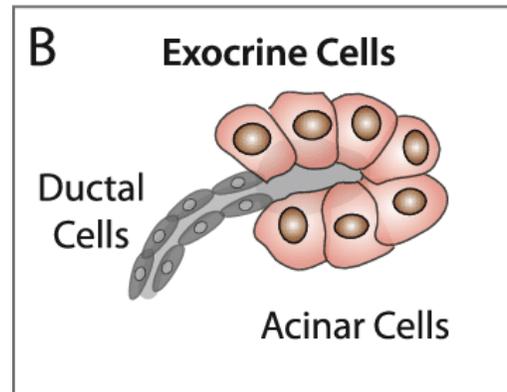
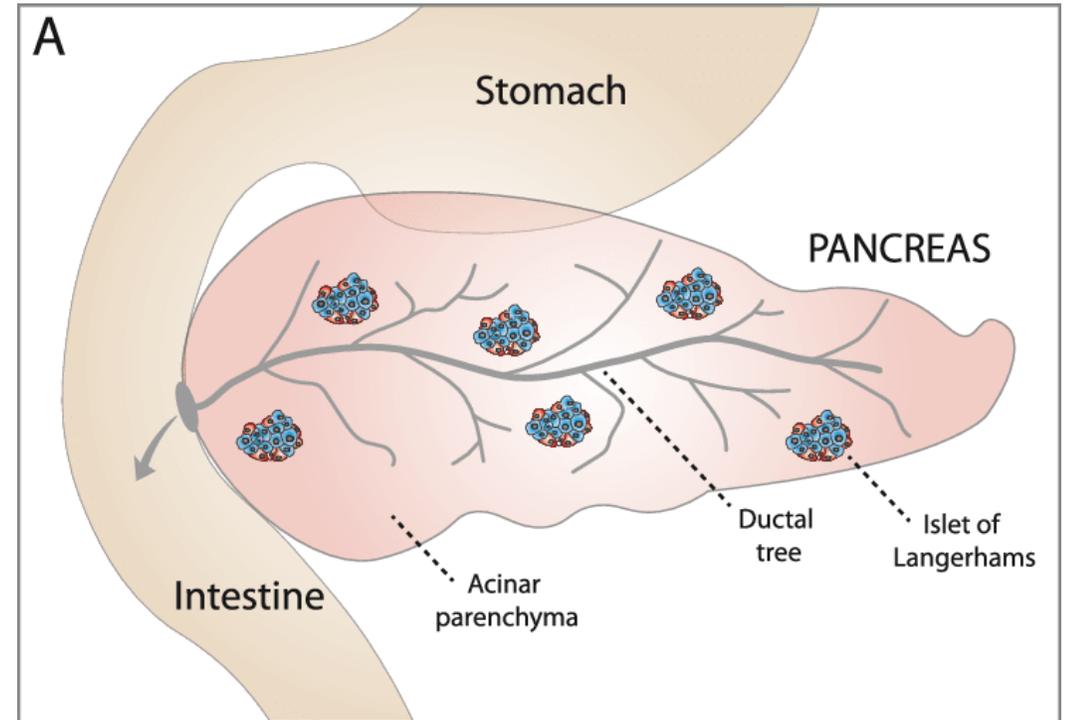


Source: Niederhaus, S. V et al. (2013). Acute cellular and antibody-mediated rejection of the pancreas allograft: incidence, risk factors and outcomes. *American Journal of Transplantation*. 13(11), 2945–2955.

Histological Assessment – Exocrine vs. Endocrine

The pancreas consists of two compartments...

1. Exocrine (95%)
2. Endocrine (5%)



Histological Assessment – Exocrine vs. Endocrine

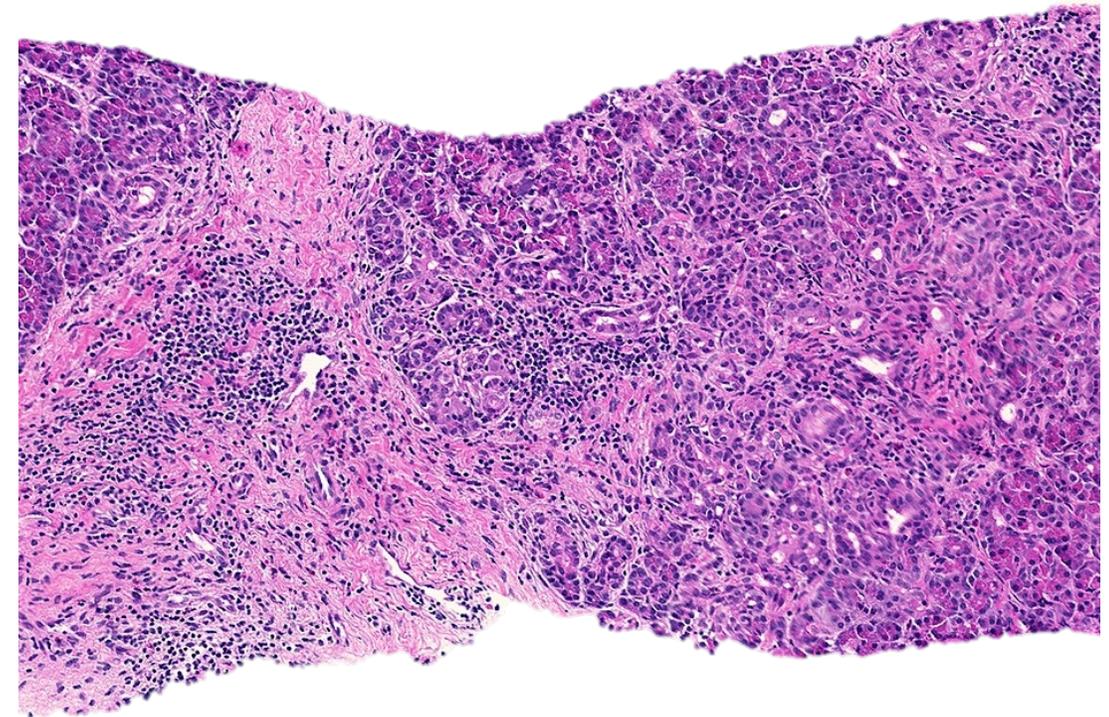
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Histologic Assessment →



“... islets are generally not involved in the rejection process. The presence of islets in pancreatic core biopsies is not necessary for determining allograft rejection or diagnosing biopsy specimens...” – Banff Schema for Grading Pancreas Allograft Rejection



Banff Classification: T Cell Mediated Rejection (TCMR) Grade II

Endocrine compartment (islets) is generally considered to be spared in acute rejection episodes!

Immunohistochemistry Staining (DAB)

Histological (Banff) Diagnosis: TCMR2
Specific for CD3 (T Lymphocytes & NK cells)



Immunohistochemistry Staining (DAB)

Histological (Banff) Diagnosis: TCMR2
Specific for Insulin



Immunohistochemistry Staining (DAB)

Histological (Banff) Diagnosis: TCMR2
Specific for CD3 (T Lymphocytes & NK cells)



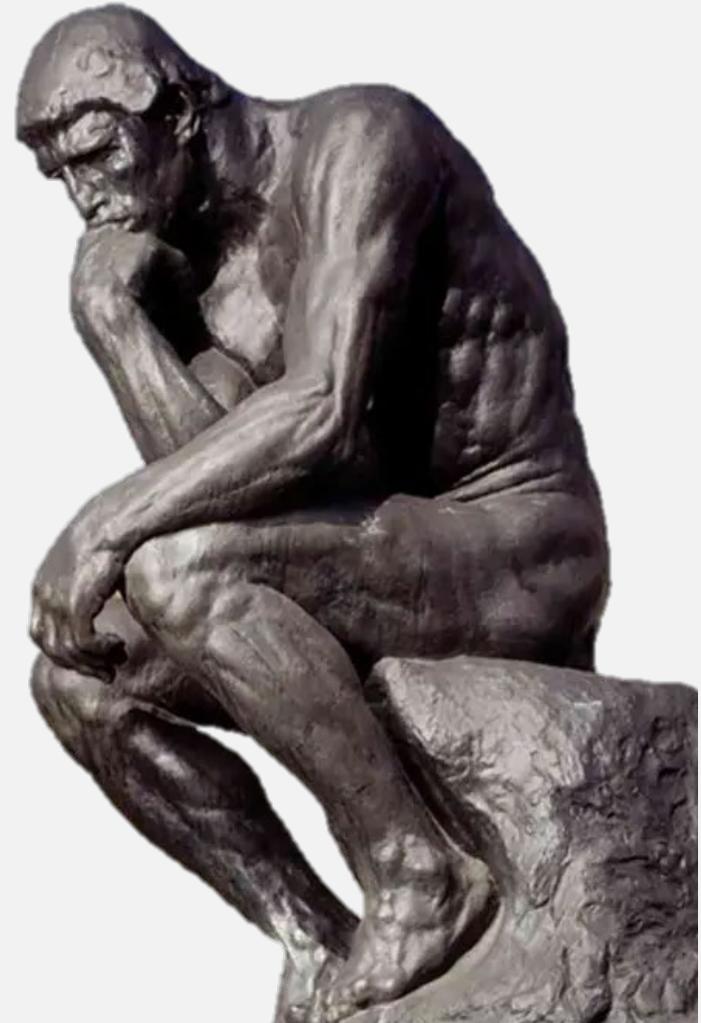
If the islets are spared...

Why do some grafts fail after rejection?

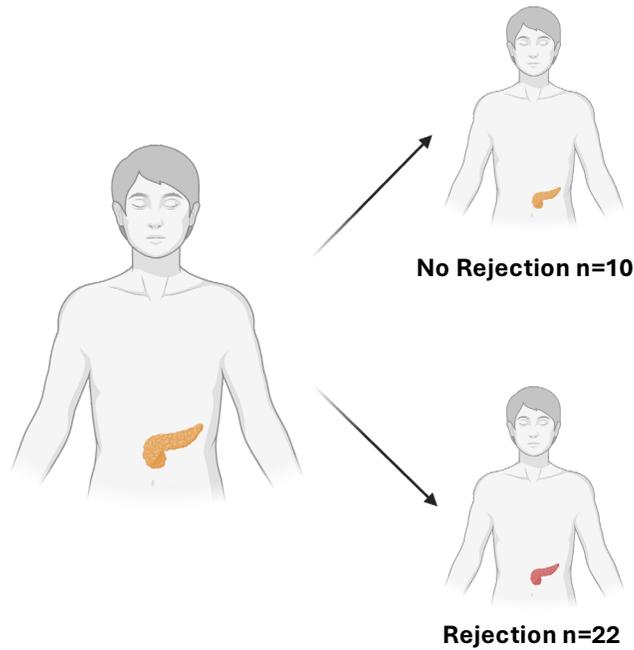
**Why do some patients develop
hyperglycemia during rejection episodes?**

Maybe...

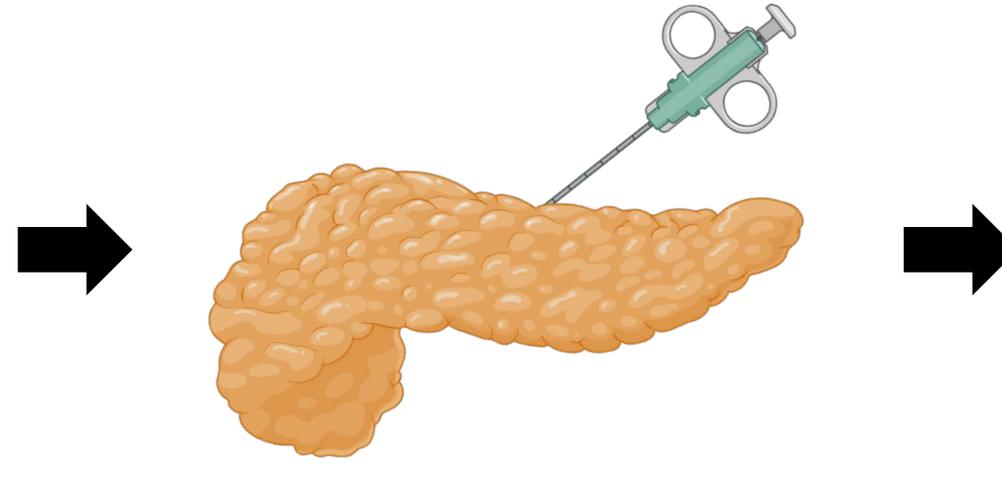
**Something is happening in the islets, we
just cant see it**



Methods



**32 Pancreas Transplant Recipients @
Hospital Clinic Barcelona**

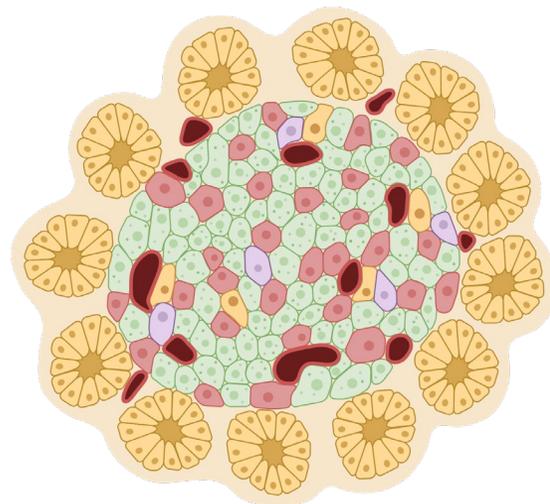


- Pancreas biopsies**
- Per protocol (3 weeks & 12 months)
 - For cause

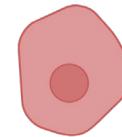
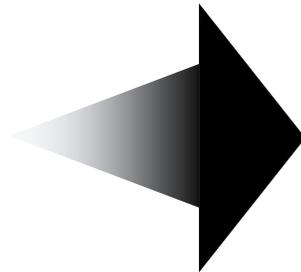
**RNA extracted from formalin-fixed
paraffin embedded (FFPE) biopsies
and Bulk RNAseq performed on
16,743 coding genes**

Generation of human islet cell type -specific identity genesets

van Gurp et al. Nature Communications, April 2022



Pancreatic Islet Specific Genes
N = 259



Alpha (α) Cell Specific Genes
N = 99



Beta (β) Cell Specific Genes
N = 101



Gamma (γ) Cell Specific Genes
N = 35



Delta (δ) Cell Specific Genes
N = 24

Results - Population Characteristics

Category	Rejection N=22	No Rejection N=10	P value
Donor			
Male Gender	12 (55%)	6 (60%)	0.773
Age (years)	32.6 ± 13.3	22.9 ± 7.1	0.039
Donation after Brain Death (DBD)	21 (96%)	10 (100%)	0.493
Cold Ischemia Time Pancreas (minutes)	685 [570-823]	480 [425 – 642]	0.003
Recipient			
Male Gender (%)	13 (59%)	3 (30%)	0.127
Age (years)	40.0 ± 8.1	40.1 ± 6.1	0.768
Dialysis Type			0.155
Hemodialysis	15 (68%)	4 (40%)	
Peritoneal Dialysis	0 (0%)	1 (10%)	
Pre-emptive	7 (32%)	5 (50%)	
Dialysis Vintage (months)	27.1 [15.2-37.5]	10.6 [7.6-26.9]	0.124
Diabetes Type			0.030
Type 1	22 (100%)	8 (80%)	
Type 2	0 (0%)	2 (20%)	
Diabetes Vintage	27.2 ± 9,7	23.3 ± 10.4	0.308
Transplant Type			0.782
SPK	12 (55%)	6 (60%)	
PAK	9 (41%)	4 (40%)	
PTA	1 (4,5%)	0 (0)	

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Results - Biopsy Characteristics

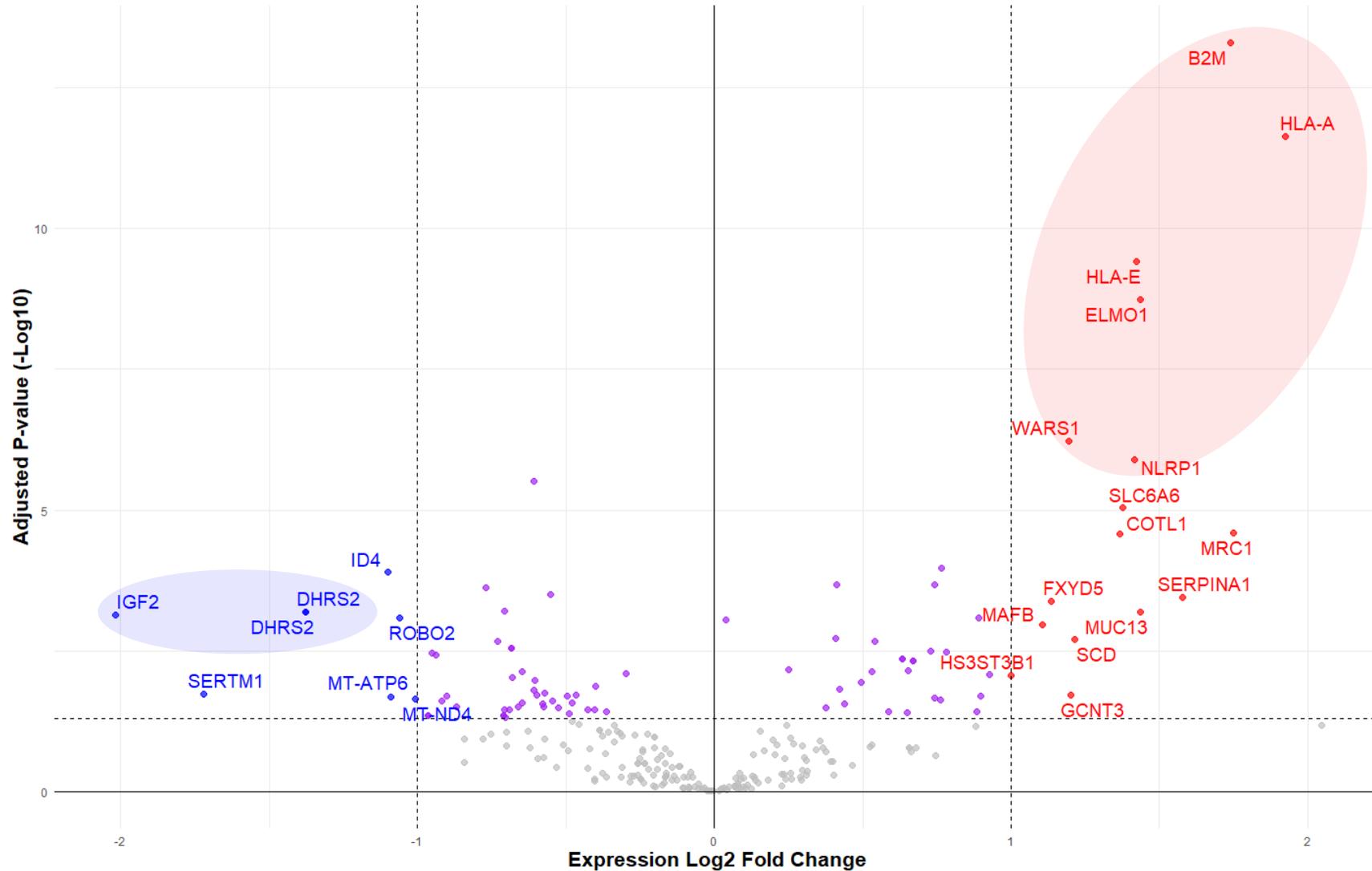
Category	Rejection N=22	No Rejection N=10	P value
Age at time of Biopsy	43.6 ± 9.41	41.9 ± 6.44	0.611
Time between Transplant & Biopsy	12.0 [5.0 – 67.5]	12.0 [1.0 – 12.5]	0.269
Biopsy on Indication	20 (91%)	4 (40%)	0.004
cPRA Total at time of Biopsy	0.0 [0.0 – 37.8]	2.5 [0.0 – 47.8]	0.633
Histology			
Islet Inflammation	3 (14%)	0 (0%)	0.553
Septal Inflammation	19 (86%)	5 (50%)	0.011
Acinar Inflammation	19 (86%)	5 (50%)	0.001
Acinar Necrosis	4 (18%)	0 (0%)	0.001
Arteritis	10 (46%)	0 (0%)	0.048
Venulitis	17 (77%)	0 (%)	<0.001
Ductitis	16 (73%)	0 (0%)	<0.001
Fibrosis	9 (43%)	1 (10%)	0.131
Biopsy Classification (Banff)			
Cellular Rejection Grade 1	6 (27,3%)	0 (0%)	
Cellular Rejection Grade 2	13 (59,1%)	0 (0%)	
Cellular Rejection Grade 3	1 (5%)	0 (0%)	
No Rejection	0 (0%)	10 (100%)	

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Results – Islet Specific Genes

Rejection vs. No Rejection



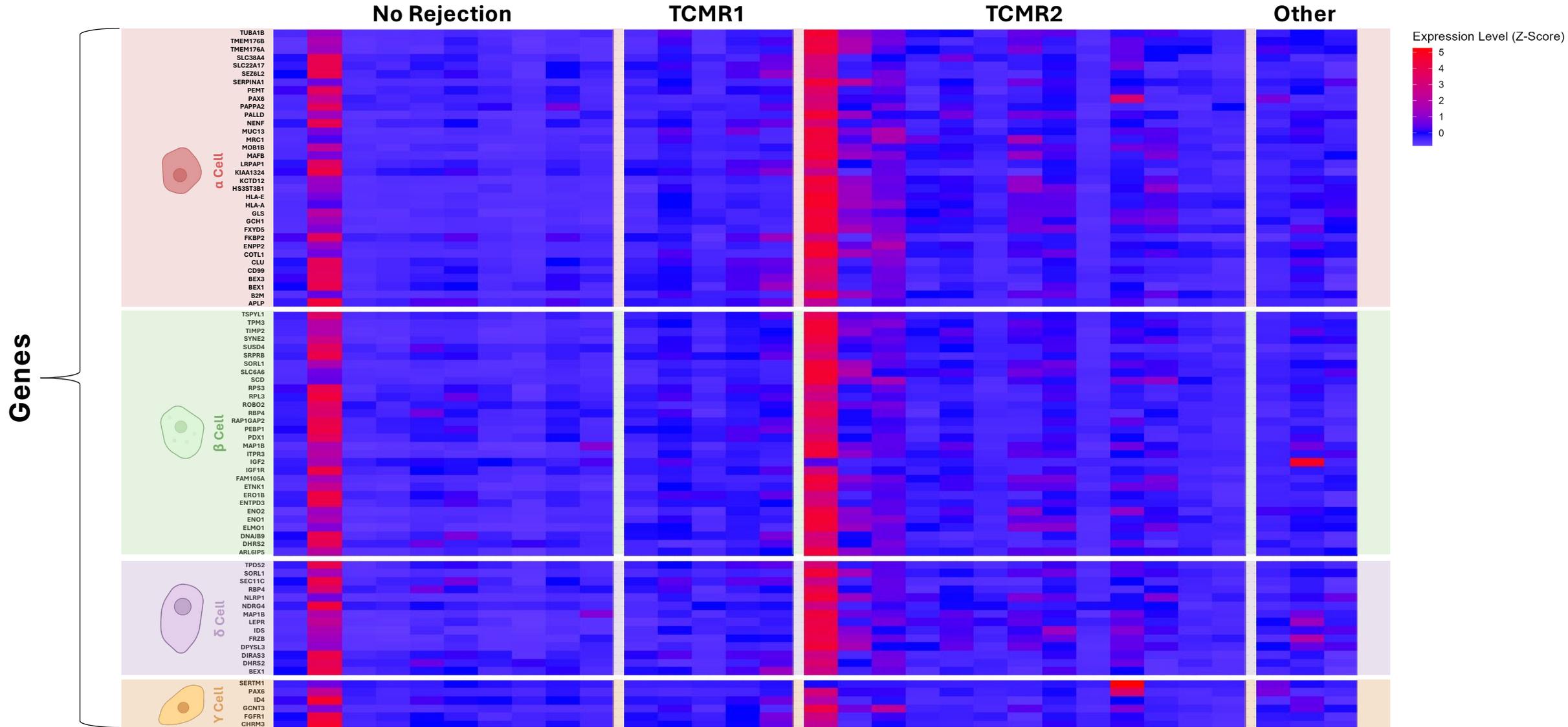
Overexpressed

- B2M
- HLA-A
- HLA-E
- ELMO1
- WARS1
- NLRP1
- FXJD5
- COTL1
- MRC1
- SERPINA1
- SLC6A6

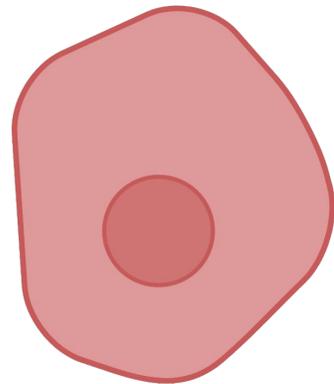
Underexpressed

- DHRS2
- ID4
- IGF2
- MT-ATP6
- MT-ND4
- ROBO2
- SERTM1

Results – Significant Islet Specific Genes



Results – Islet α Cell Pathways



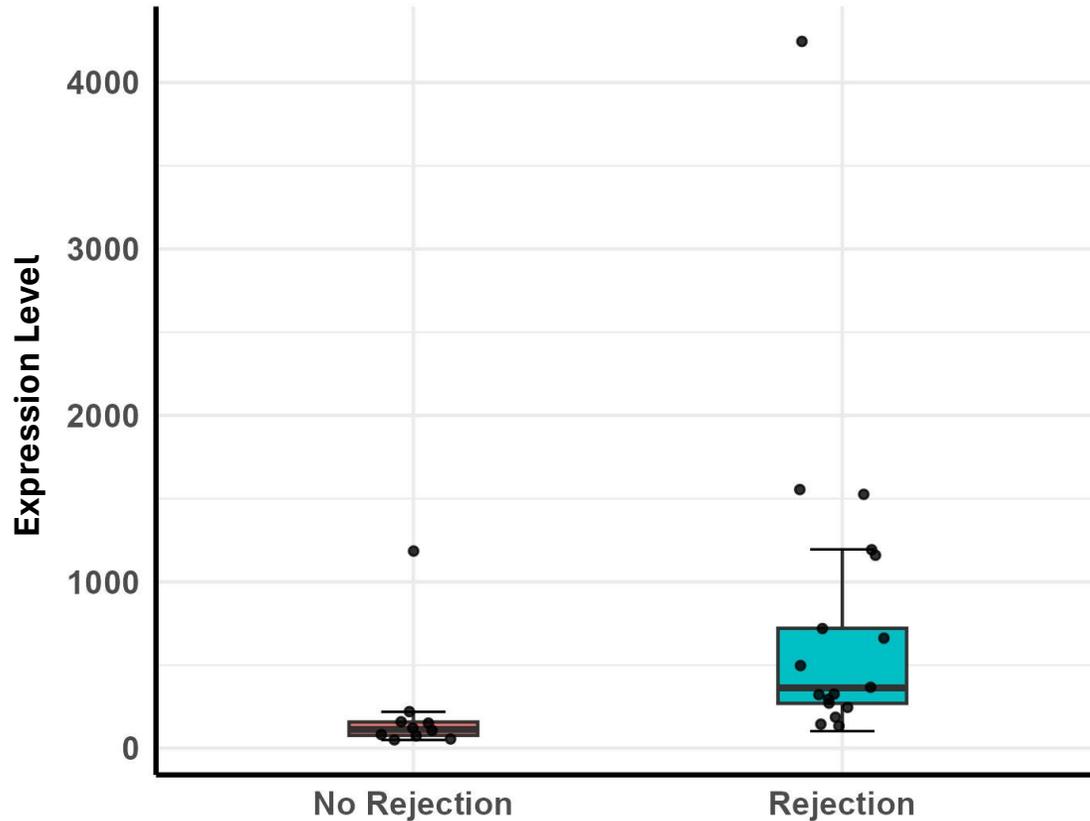
α Cell

Expression	Gene	Change	Pathway
↑	TMEM176A	0.928	Protein Processing & Secretion
	GLS	0.540	Cellular Metabolism & Energy Regulation
	GCH1	0.890	
	TUBA1B	0.655	Structural & Cytocellular Components
	FXYD5	1.134	Cell Adhesion, Migration & Communication
	MUC13	1.434	
	HS3ST3B1	1.001	
	KCTD12	0.742	
↓	PAX6	-0.682	Development & Differentiation
	APLP1	-0.951	Stress Response & Apoptosis

***Immune/Inflammation pathways omitted**

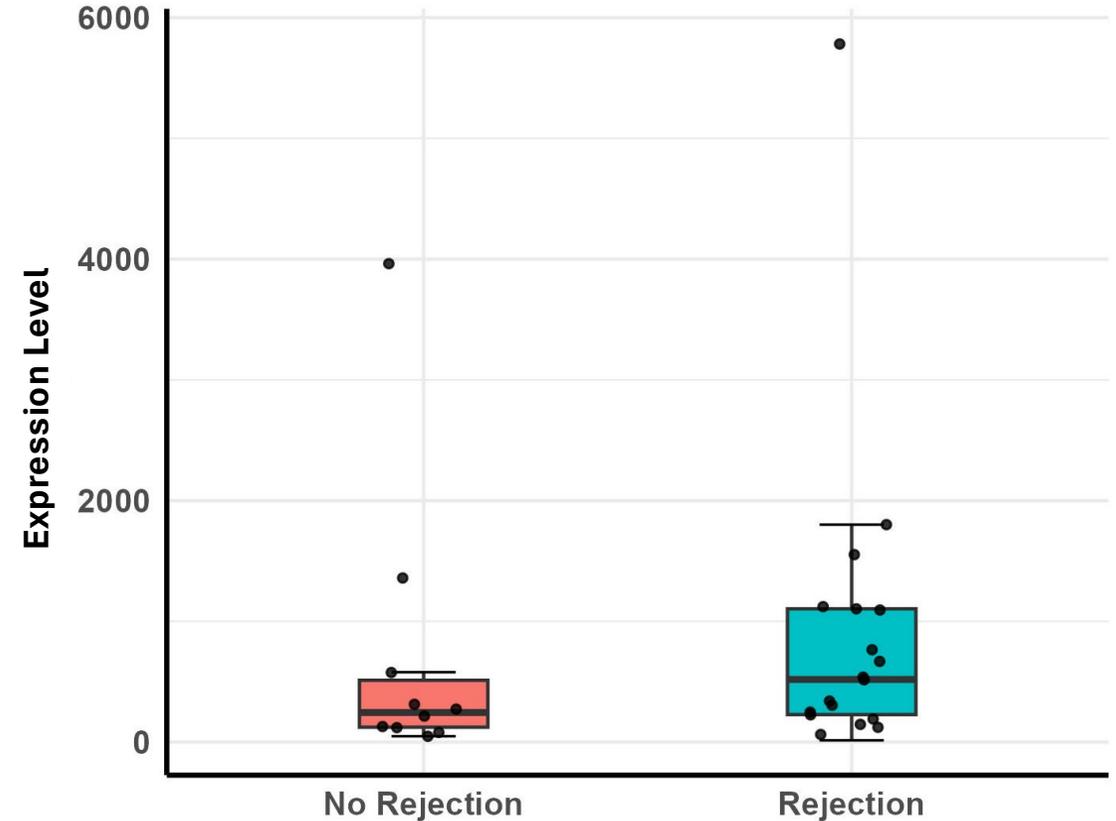
Results – Islet α Cell Pathway Genes

MAFB Expression



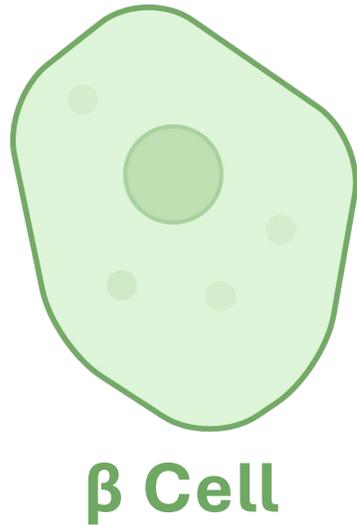
Encodes: **MAF BZIP Transcription Factor B**
Role in α cell: **Activates the glucagon gene promoter, ensuring proper glucagon production and secretion.**

TTR Expression



Encodes: **Transthyretin**
Role in α cell: **Regulates glucagon release through secretory vesicles and acts as a positive regulator of alpha cell function.**

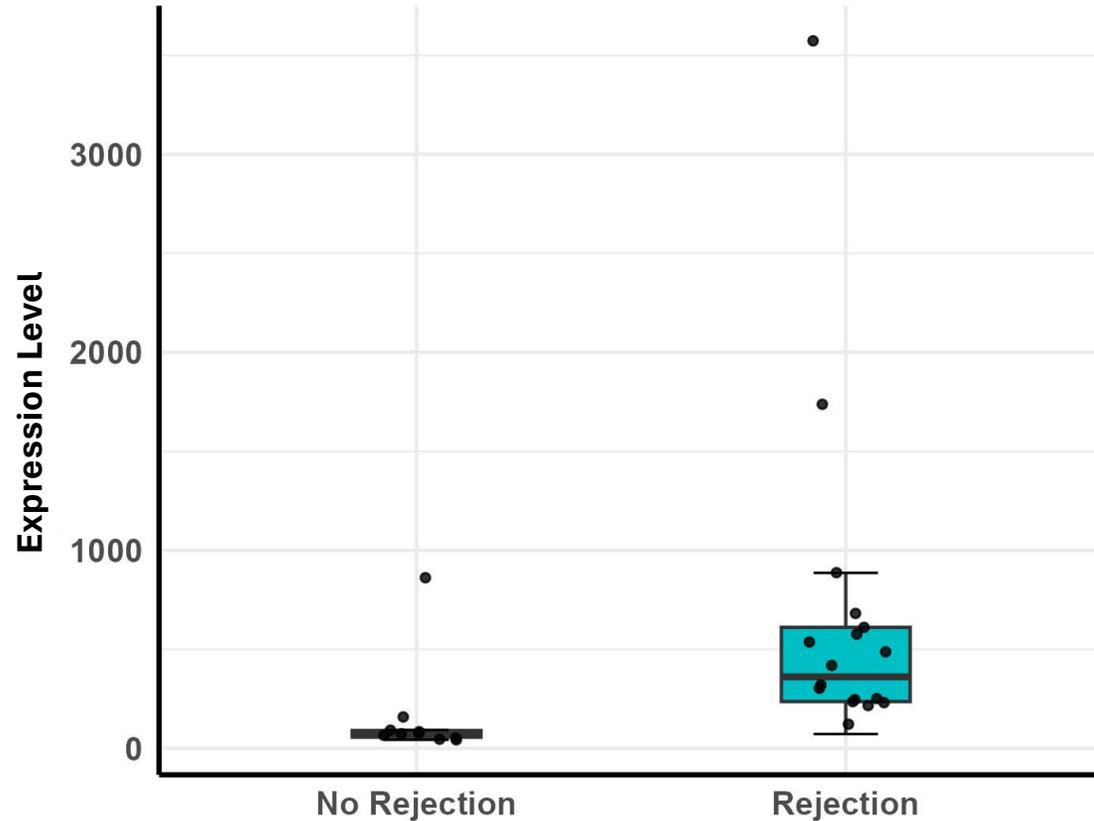
Results – Islet β Cell Pathways



Expression	Gene	Change	Pathway
↑	SLC6A6	1.376	Cellular Metabolism & Energy Regulation
	SCD	1.213	
	ENO2	0.781	
	ELMO1	1.437	Cell Adhesion, Migration & Communication
	SORL1	0.633	
↓	TSPYL1	-0.298	Insulin Secretion & β Cell Function
	IGF1R	-0.608	
	IGF2	-2.018	
	RAP1GAP1	-0.551	Stress Response & Apoptosis
	DHRS2	-1.375	

Results – Islet β Cell Pathways

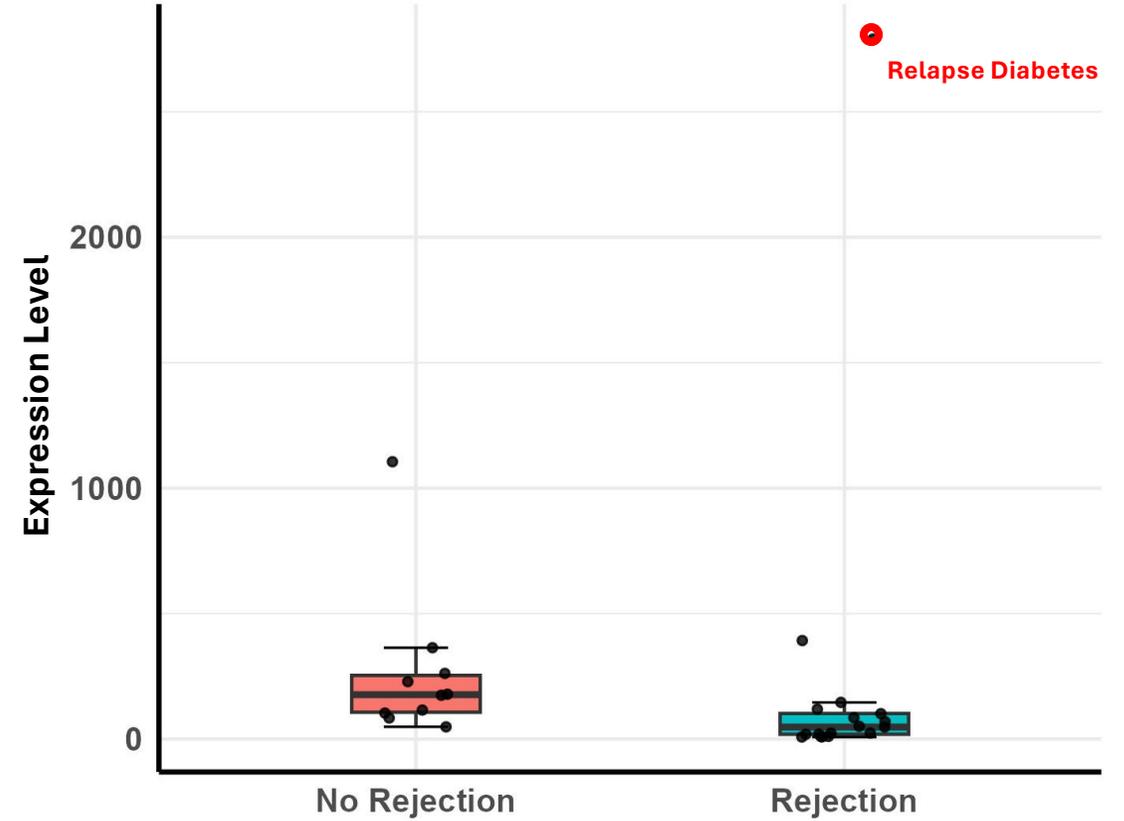
SLC6A6 Expression



Encodes: **Taurine Transporter (TauT)**

Role in β cell: **Facilitates uptake of taurine, supporting osmoregulation, antioxidation, and modulation of calcium signaling.**

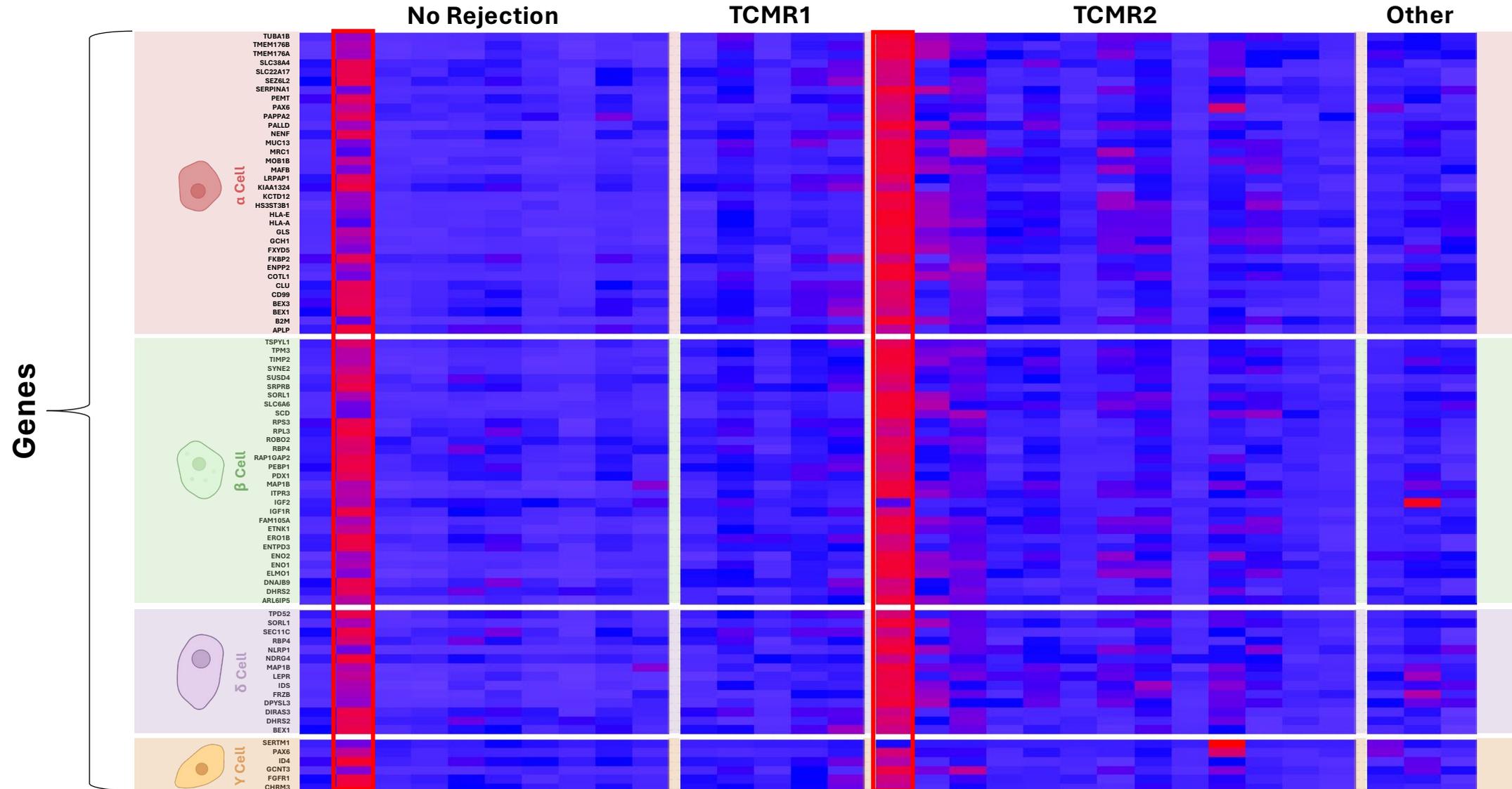
IGF2 Expression



Encodes: **Insulin Growth Factor 2**

Role in β cell: **Promotes beta cell growth, survival, and stress protection, especially during inflammation/metabolic stress.**

Results – Whats happening here?



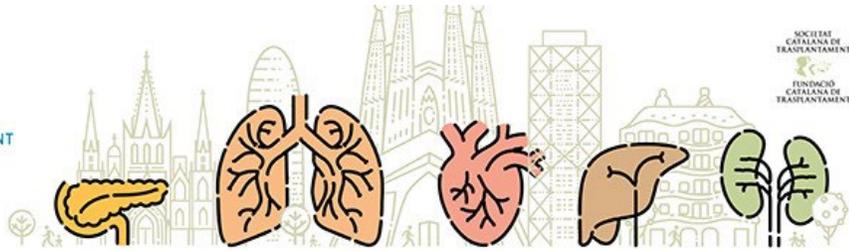
- **Islet injury occurs during T-cell mediated rejection**, even when islets appear histologically spared — suggesting that molecular stress precedes or accompanies visible damage.
- **Severity matters:** Gene markers of islet injury are more strongly expressed in higher-grade rejection (Grade 2/3 TCMR), pointing to a dose-response relationship between immune activation and islet stress.
- **Type 2 diabetes recipients may show early islet stress**, independent of rejection — possibly due to underlying metabolic or inflammatory factors.
- These findings highlight a **hidden layer of graft vulnerability**, which is not captured by conventional histology.
- Further studies are needed to explore the **clinical significance** of islet-specific gene expression patterns — particularly for **predicting graft outcomes**.

Acknowledgements



FRCB IDIBAPS	Hospital Clinic Barcelona	University Medical Center Groningen	Rey Juan Carlos University
Fritz Diekmann	Joana Ferrer-Fàbrega	Robert Pol	Alejandro Álvaro-Meca
Pedro Ventura-Aguar	Ivan Archilla	Stephan Bakker	
Maria Jose Ramirez	Maria Angeles Garcia-Criado		
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