Beta-Cell Workload Hypothesis: Diabetes Progression Model

Demand < Capacity ——————————> *Demand >> Capacity*

NORMAL	COMPENSATION	STRESS	EXHAUSTION	FAILURE
CWI < 0.3	*CWI 0.3-0.6*	*CWI 0.6-0.8*	*CWI > 0.8*	*Clinical T2D*
Low Workload Healthy Function	**Rising Workload Metabolic Strain**	**ER Stress UPR Activated**	**Dedifferentiation Identity Loss**	**Clinical T2D Beta-Cell Failure**
↑ **GCK** — Glucose sensor	↑ **GCK** — Increased	↑ **DDIT3** — CHOP/Apoptosis	↓ **PDX1** — Identity loss	↓ **Beta-cell** — Mass < 50%
↑ **SLC2A2** — GLUT2	↑ **INS** — Hyperfunction	↑ **XBP1** — UPR active	↓ **MAFA** — Immaturity	↓ **Insulin** — Secretion
↑ **PDX1** — Identity	↑ **HSPA5** — ER expansion	↑ **HSPA5** — BiP saturated	↑ **ALDH1A3** — Dediff marker	↑ **Glucose** — Hyperglycemia
↑ **MAFA** — Maturation		↑ **ATF4** — Stress TF	↑ **SOX9** — Progenitor	
Insulin secretion matches demand	43 metabolic bottlenecks emerge	Protein folding overload	Beta cells lose mature phenotype	Fasting glucose > 126 mg/dL

Evidence Sources:

MR Analysis

GEM Model

DisGeNET

LINCS

Chronic metabolic demand exceeding capacity drives progressive dysfunction

Low   High

Composite Workload Index (CWI)