

Pathophysiology of Type 1 Diabetes



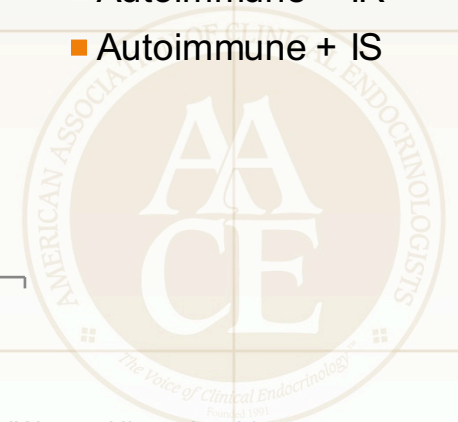
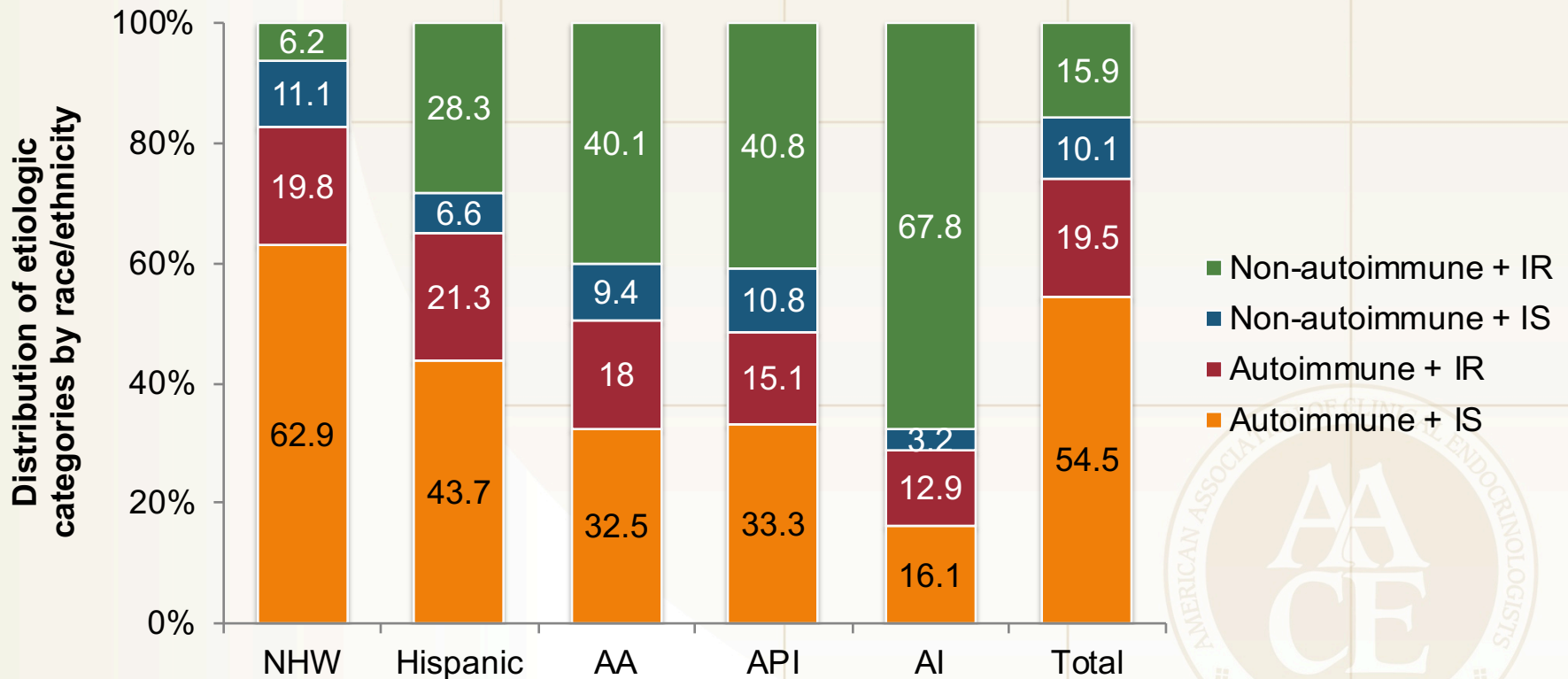
Type 1 Diabetes Mellitus

- Characterized by absolute insulin deficiency
- Pathophysiology and etiology
 - Result of pancreatic beta cell destruction
 - Prone to ketosis
 - Total deficit of circulating insulin
 - Autoimmune
 - Idiopathic



Type of Diabetes in Youth by Race/Ethnicity and Etiology

SEARCH for Diabetes in Youth Study
(N=2291)

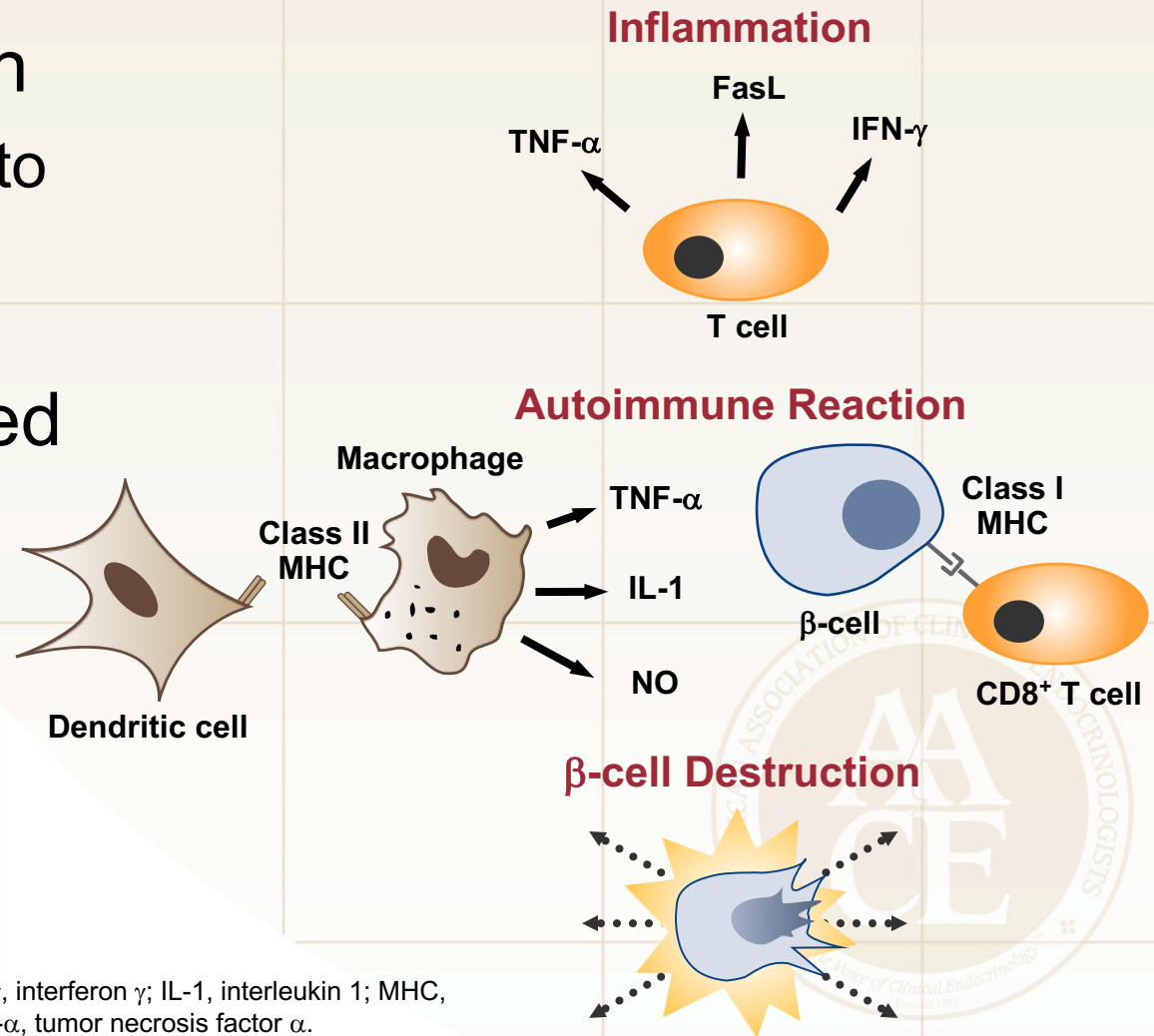


AA, African American; AI, American Indian; API, Asian/Pacific Islander; IR, insulin resistant; IS, insulin sensitive; NHW, non-Hispanic white.

Dabelea D, et al. *Diabetes Care*. 2011;34:1628-1633.

Type 1 Diabetes Pathophysiology

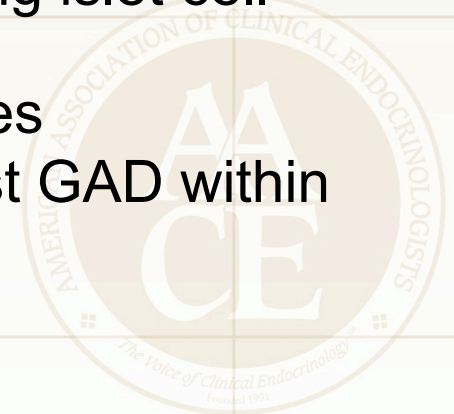
- β -cell destruction
 - Usually leading to absolute insulin deficiency
- Immune mediated
- Idiopathic



CD8, cluster of differentiation 8; FasL, Fas ligand; IFN- γ , interferon γ ; IL-1, interleukin 1; MHC, major histocompatibility complex; NO, nitric oxide; TNF- α , tumor necrosis factor α .

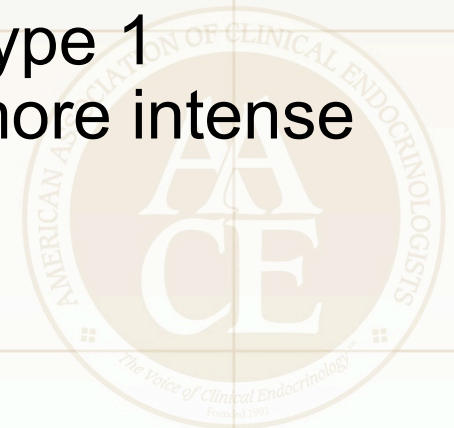
Pathophysiologic Features of Type 1 Diabetes

- Chronic autoimmune disorder
 - Occurs in genetically susceptible individuals
 - May be precipitated by environmental factors
- Autoimmune response against
 - Altered pancreatic β -cell antigens
 - Molecules in β -cells that resemble a viral protein
- Antibodies
 - Approximately 85% of patients: circulating islet cell antibodies
 - Majority: detectable anti-insulin antibodies
 - Most islet cell antibodies directed against GAD within pancreatic β -cells

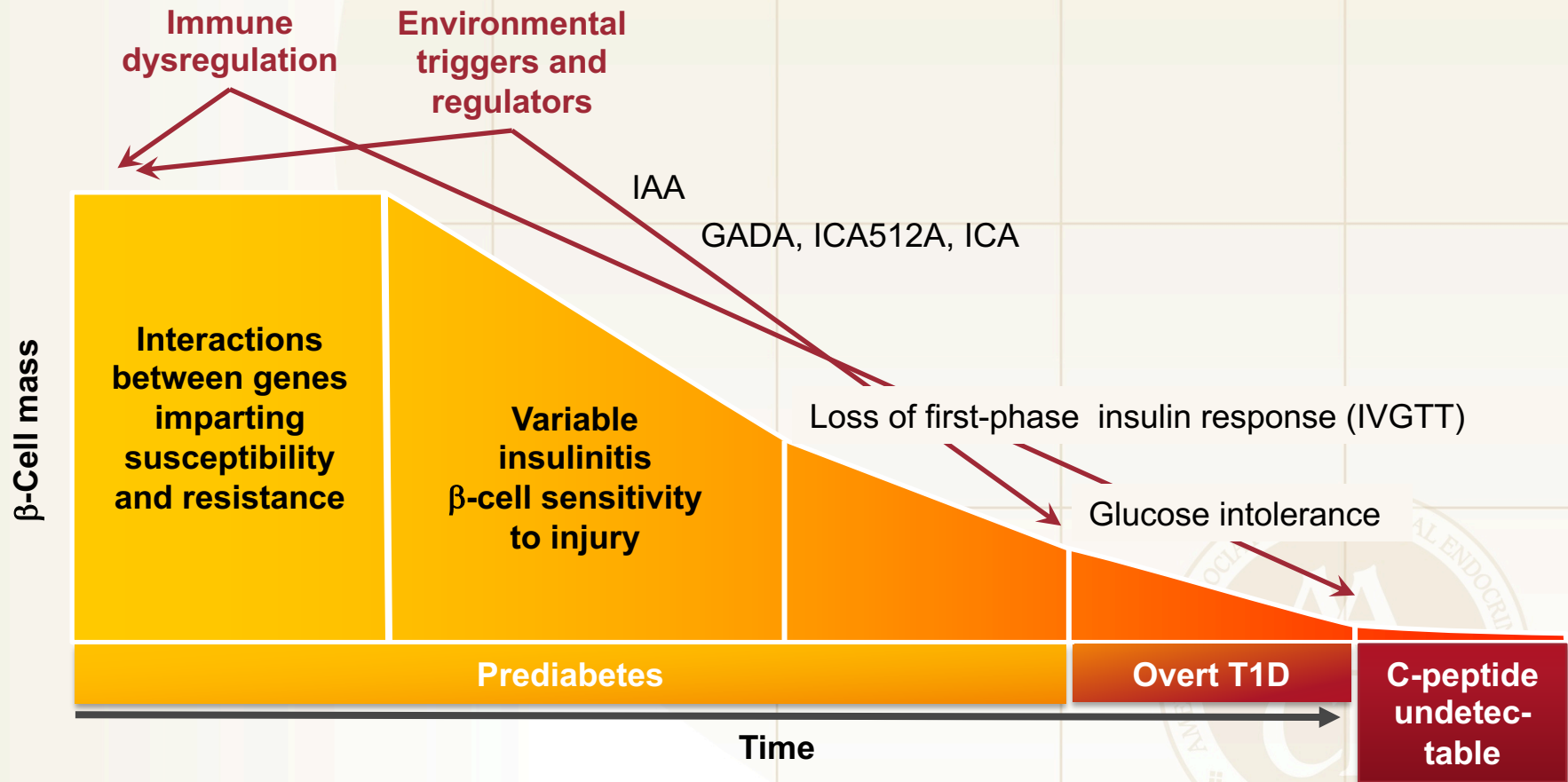


Trends in T1D Immunophenotype at Diagnosis

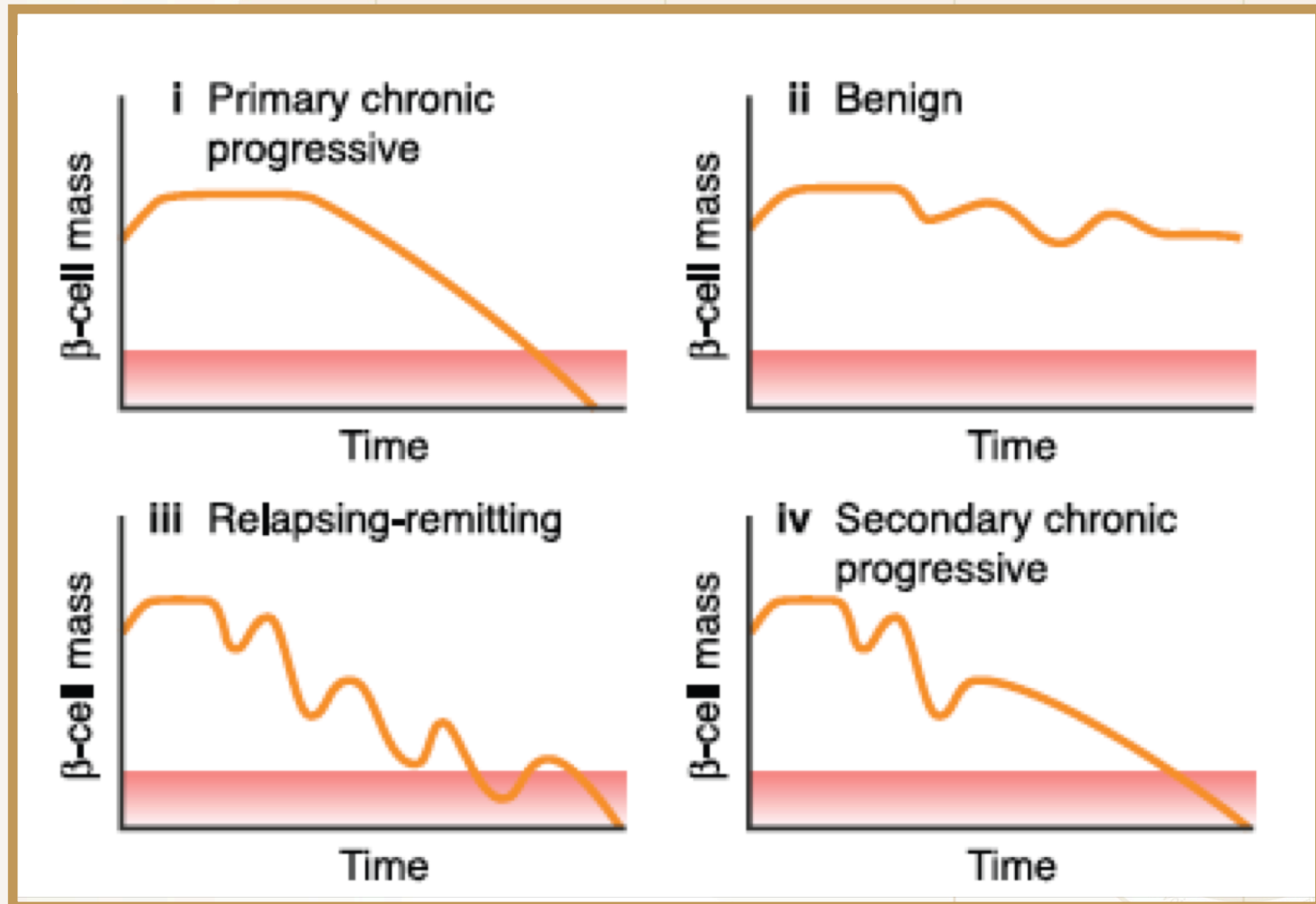
- Prevalence of IA-2A and ZnT8A has increased significantly, mirrored by raised levels of IA-2A, ZnT8A, and IA-2 β autoantibodies (IA-2 β A)
- IAA and GADA prevalence and levels have not changed
- Increases in IA-2A, ZnT8A, and IA-2 β A at diagnosis during a period of rising incidence suggest that the process leading to type 1 diabetes is now characterized by a more intense humoral autoimmune response



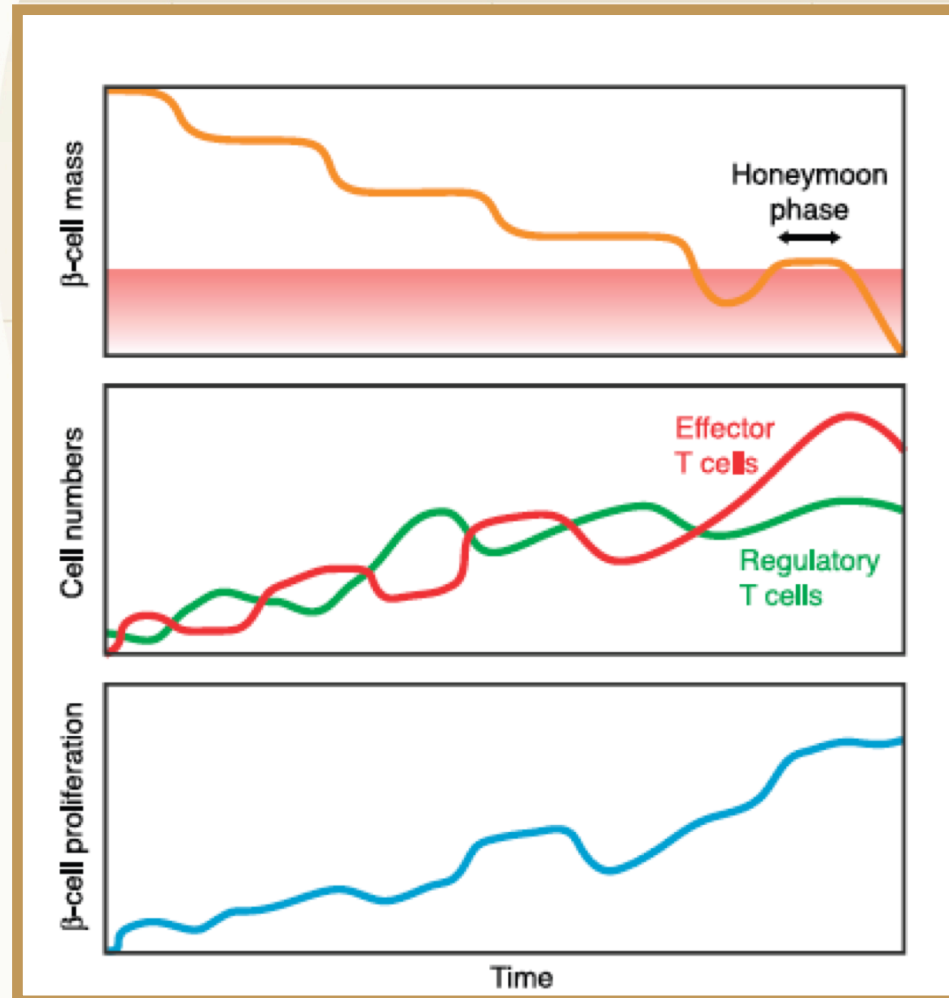
Autoimmune Basis for Type 1 Diabetes



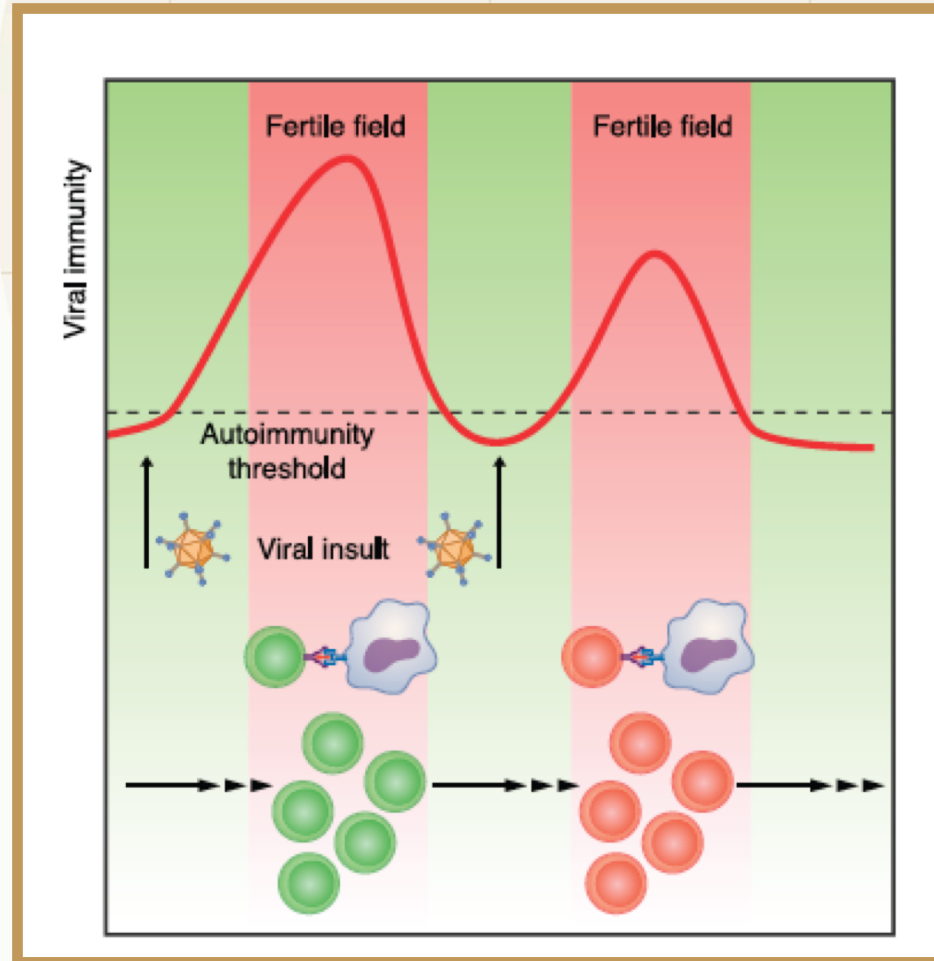
Models for Pathogenesis of T1D



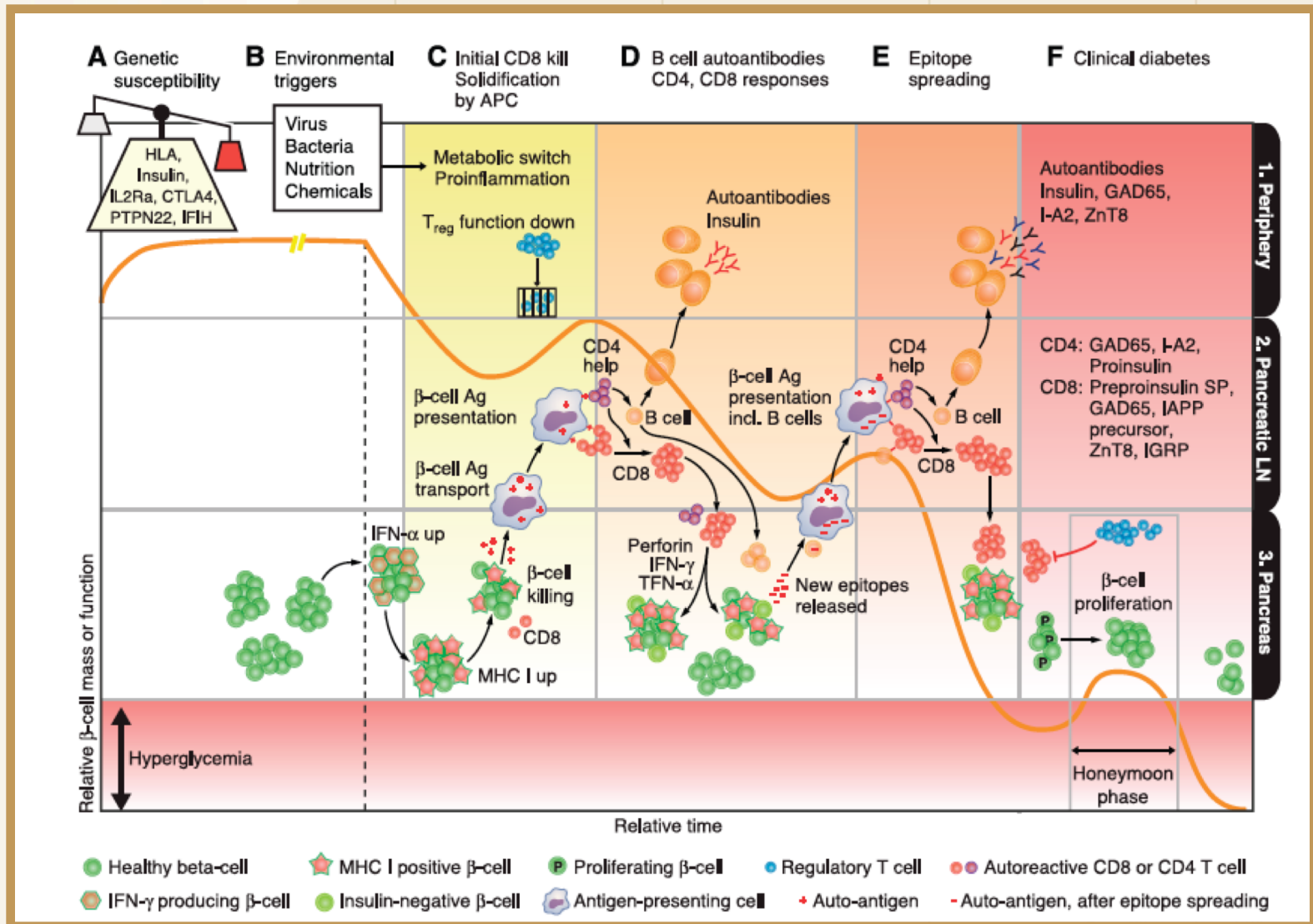
Models for Pathogenesis of T1D



Models for Pathogenesis of T1D: Fertile Field Hypothesis



How Type 1 Diabetes Might Arise



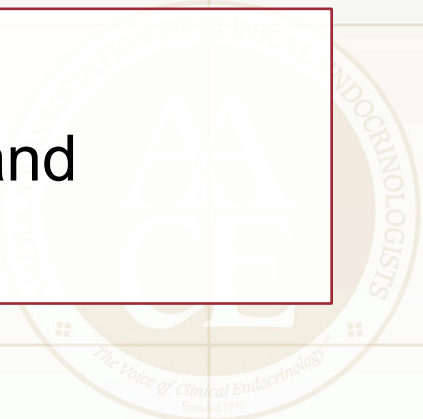
Insulin and Glucose Metabolism

Major Metabolic Effects of Insulin

- Stimulates glucose uptake into muscle and adipose cells
- Inhibits hepatic glucose production

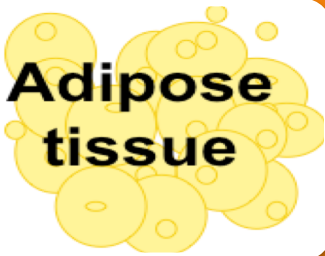
Consequences of Insulin Deficiency

- Hyperglycemia → osmotic diuresis and dehydration



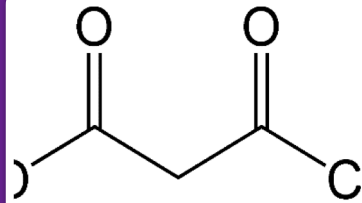
Major Metabolic Effects of Insulin and Consequences of Insulin Deficiency

Adipose tissue



Insulin effects: inhibits breakdown of triglycerides (lipolysis) in adipose tissue

- Consequences of insulin deficiency: elevated FFA levels



Insulin effects: inhibits ketogenesis

- Consequences of insulin deficiency: ketoacidosis, production of ketone bodies



Insulin effects in muscle: stimulates amino acid uptake and protein synthesis, inhibits protein degradation, regulates gene transcription

- Consequences of insulin deficiency: muscle wasting