

Mechanisms of β -Cell Destruction

Autoimmunity and the natural history of type 1 diabetes

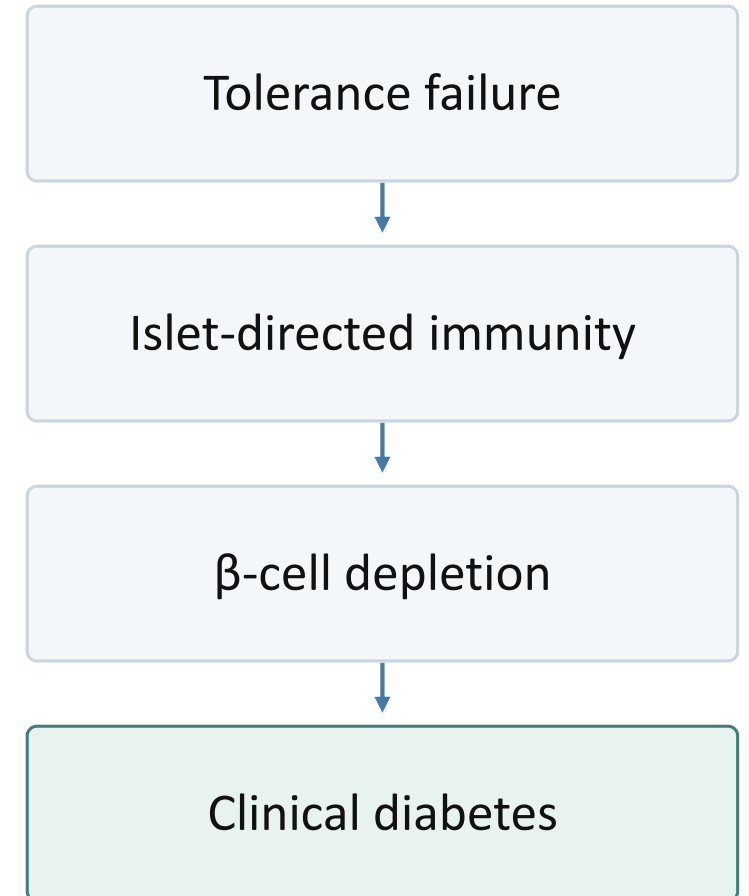
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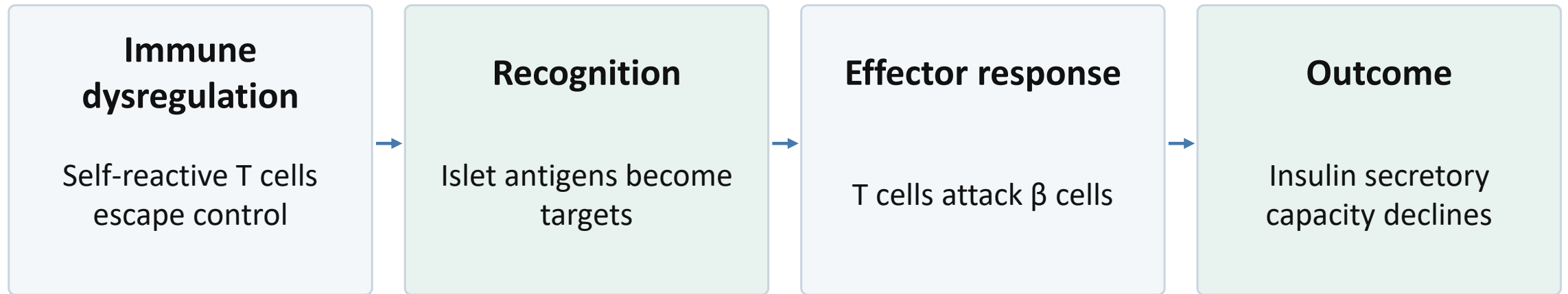
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Learning outcomes

- Trace how failure of T-cell tolerance leads to islet injury.
- Distinguish the three stages of autoimmune type 1 diabetes.
- Explain the roles of CD8⁺ T cells, Th1 cells and islet autoantibodies.
- Connect loss of β -cell reserve with insulinitis and clinical manifestations.



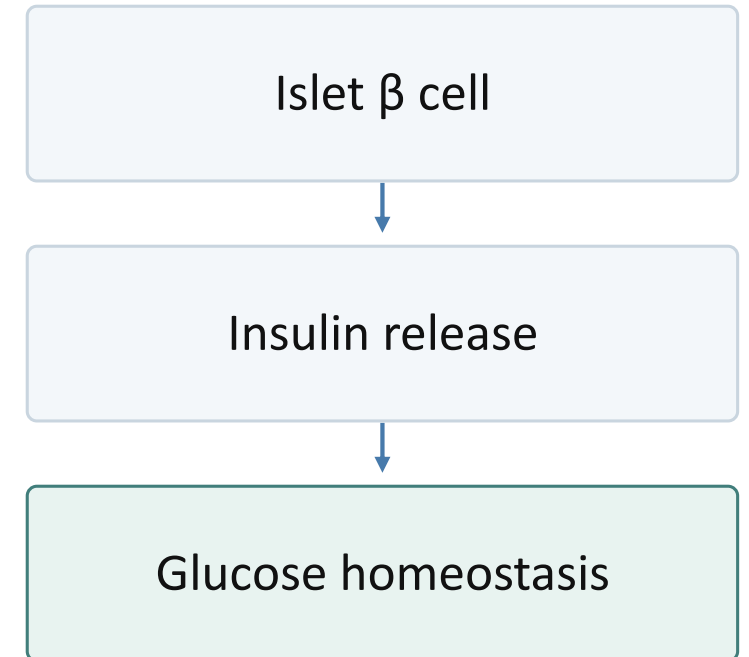
The central pathological mechanism



Type 1 diabetes is an immune-mediated β -cell disease.

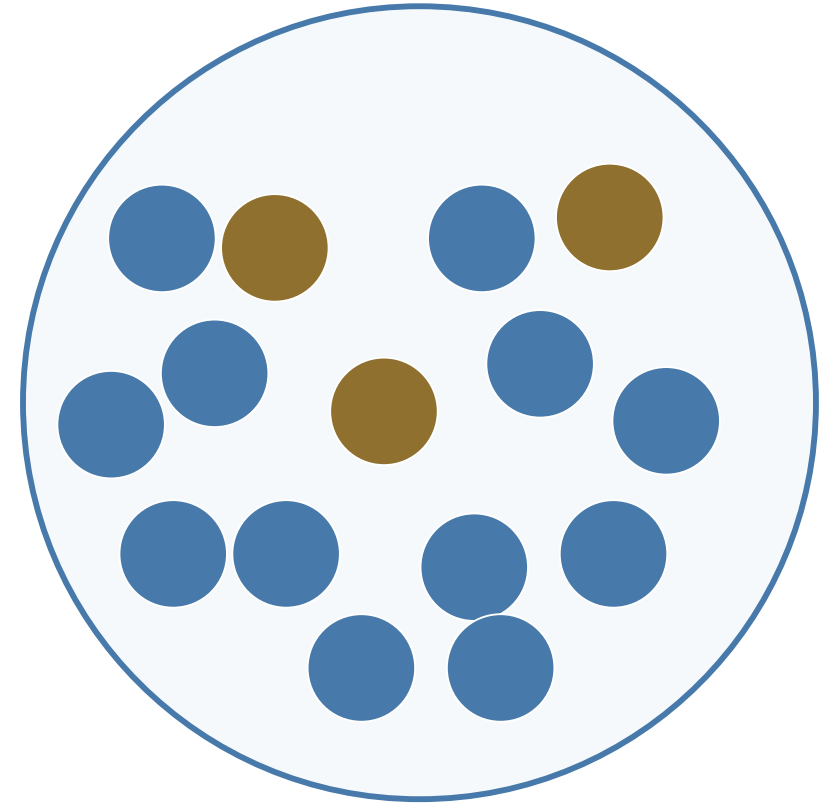
Why pancreatic β cells matter

- β cells are insulin-producing endocrine cells in the islets of Langerhans.
- Insulin promotes tissue glucose utilization and lowers circulating glucose.
- Loss of the β -cell population progressively restricts insulin secretion.
- The consequences emerge when functional reserve can no longer maintain glucose balance.



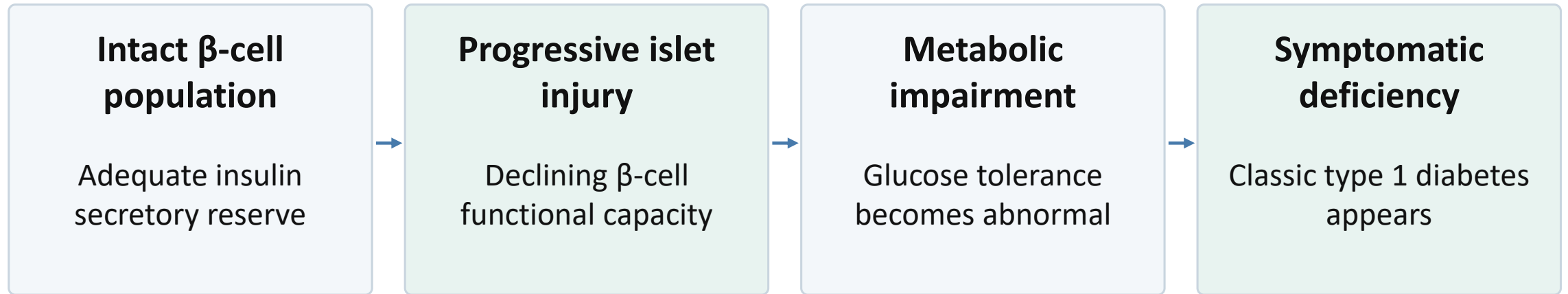
The pancreatic islet is the immune target

- The endocrine pancreas contains multiple hormone-producing cell types.
- Immune injury in type 1 diabetes is centered on insulin-producing β cells.
- An islet contains β cells alongside other endocrine cells and local vasculature.



Schematic islet; Spatial distribution is not a histologic measurement

Insulin reserve links pathology to phenotype



Clinical presentation is late relative to the initiation of autoimmunity.

Type 1 and type 2 diabetes: Different mechanisms

Type 1 diabetes

Primary immune-mediated β -cell loss

Breakdown of islet self-tolerance

Insulinitis and β -cell depletion

Type 2 diabetes

Insulin resistance with inadequate compensation

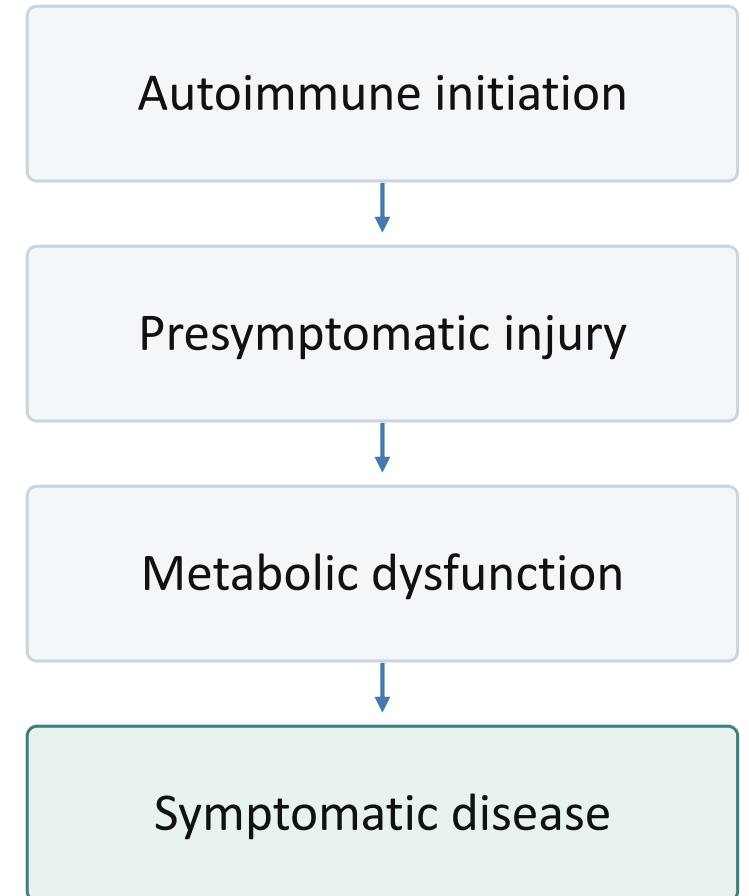
No established autoimmune basis

Islet amyloid may be present

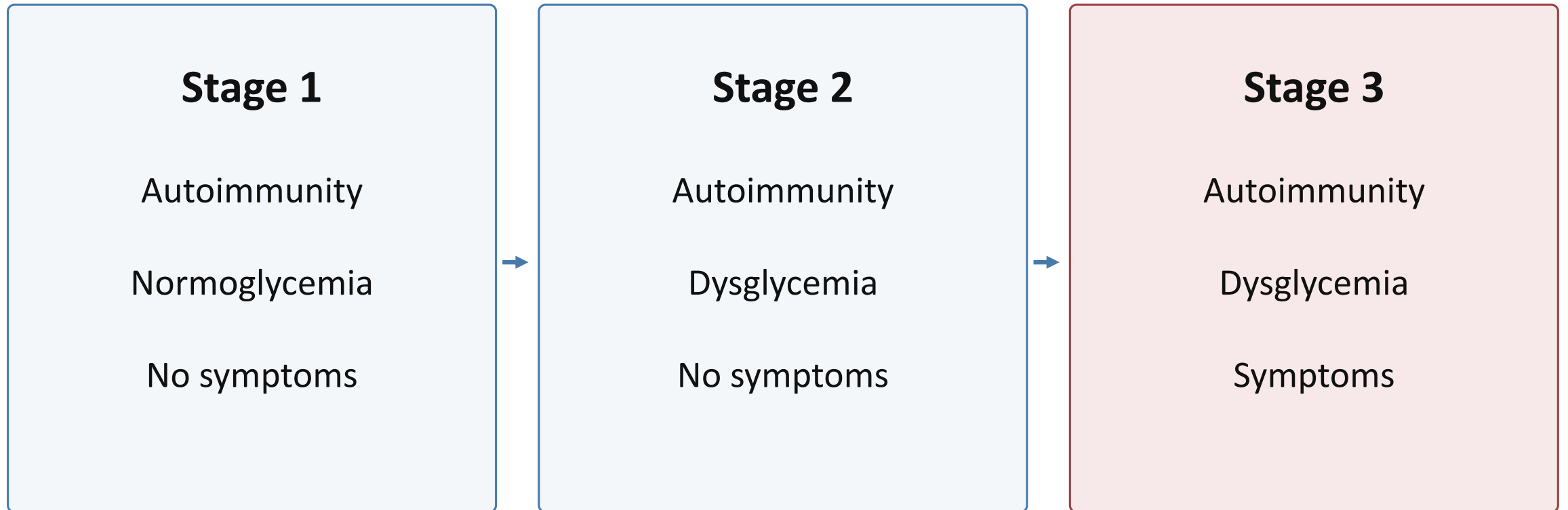
This lecture addresses autoimmune β -cell destruction, not every cause of β -cell dysfunction.

Clinical onset may conceal years of pathology

- The appearance of type 1 diabetes can be clinically abrupt.
- The islet-directed autoimmune process begins well before symptoms.
- Insulin reserve is progressively depleted during a clinically silent interval.
- Symptoms mark a later phase of an ongoing biological process.



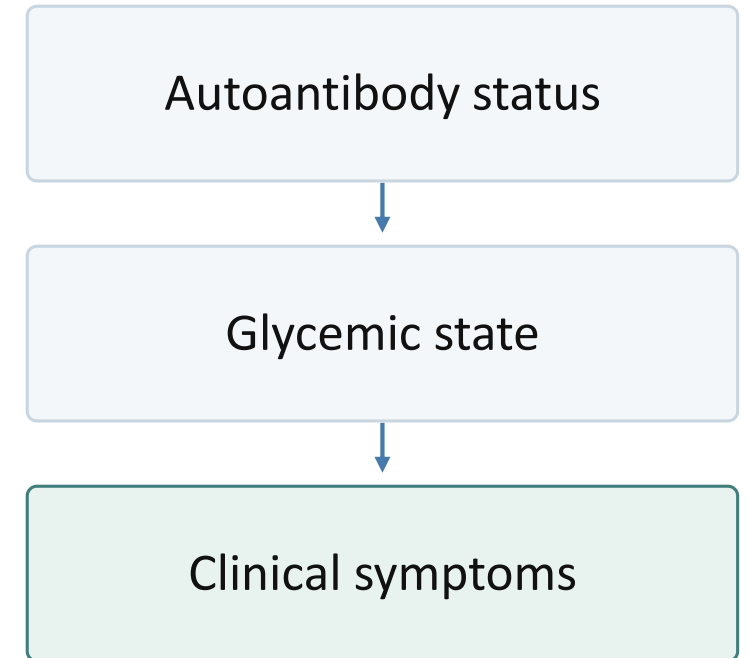
The three-stage model of type 1 diabetes



Autoimmune activity may precede both dysglycemia and symptoms.

Stage classification uses three distinct dimensions

- Islet autoimmunity: Disease-associated circulating autoantibodies.
- Glycemic status: Normoglycemia versus dysglycemia.
- Clinical status: Absence or presence of symptoms.
- A stage is defined by a pattern, not by a single isolated finding.



Stage 1: Presymptomatic autoimmunity

Immune feature

At least two islet autoantibodies are present

Evidence of established islet autoimmunity

Metabolic feature

Glucose values remain in the normal range

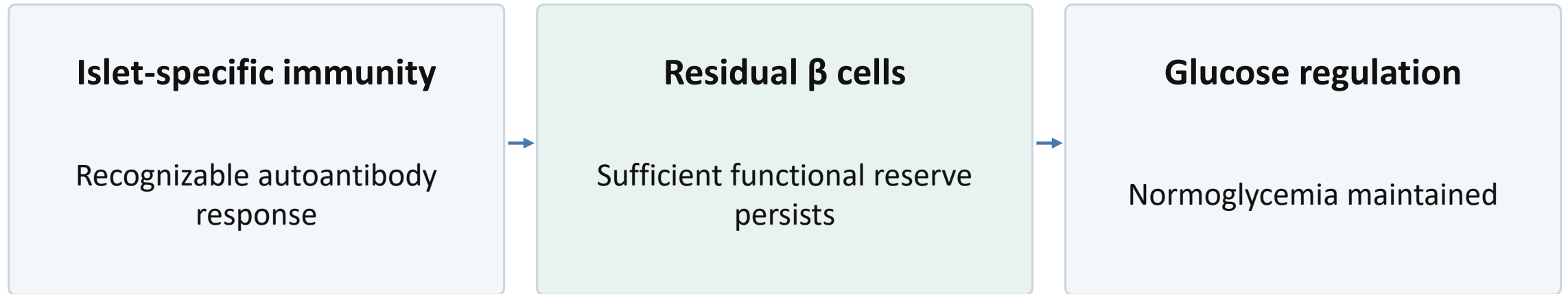
Insulin reserve still maintains glycemia

Clinical feature

No classic diabetes symptoms

Disease is biologically present but clinically silent

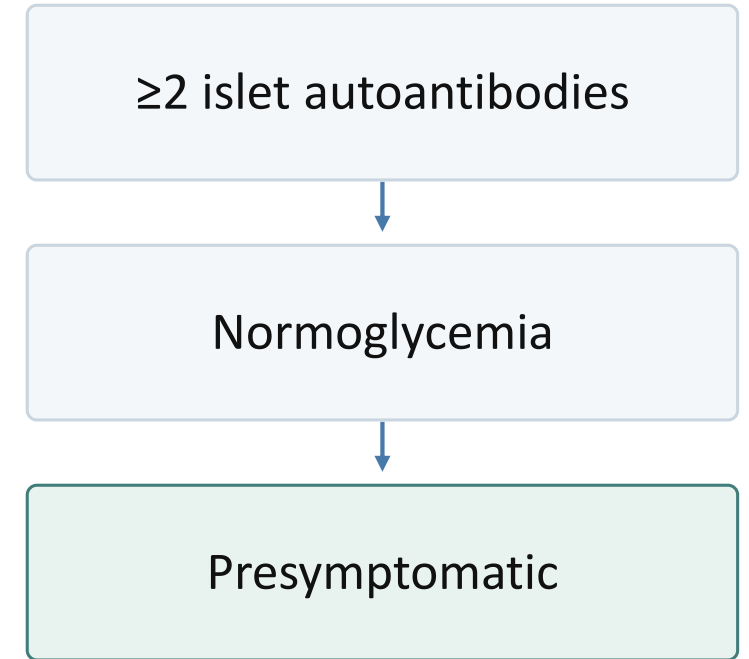
How stage 1 remains normoglycemic



Autoimmunity and hyperglycemia are not equivalent states.

Why multiple autoantibodies are informative

- The stage 1 definition requires two or more islet autoantibodies.
- Their coexistence supports a disease-associated autoimmune process.
- Autoantibodies may be detectable before any symptoms or dysglycemia.
- Their presence does not establish that antibodies are the direct mediators of cell death.



Stage 2: Dysglycemia without symptoms

Immune status

Islet autoimmunity persists

The process remains
presymptomatic

Physiologic change

Glucose tolerance becomes
increasingly impaired

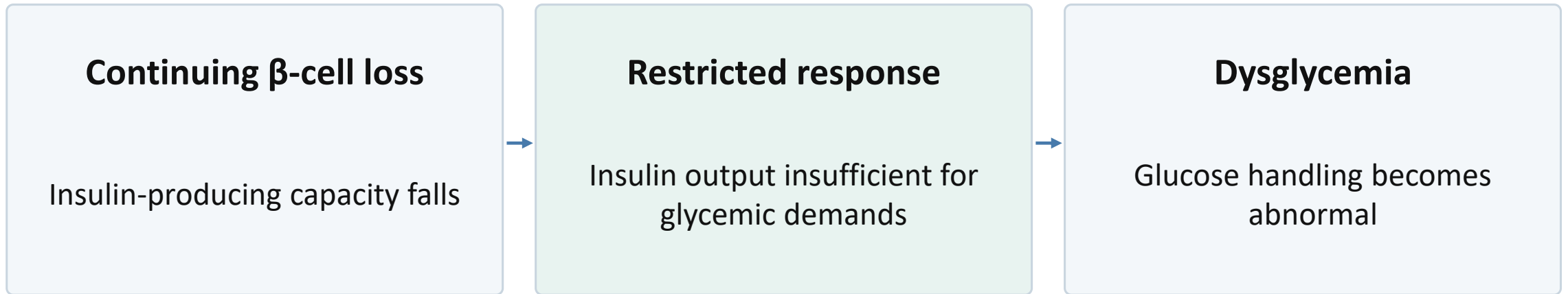
Remaining β -cell reserve no
longer fully compensates

Clinical interpretation

Dysglycemia precedes classic
symptoms

Biological progression is
underway

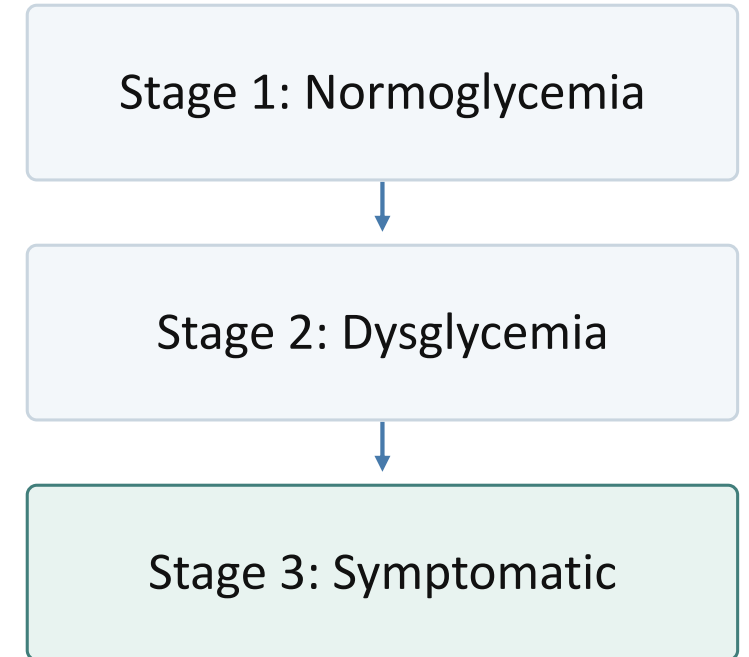
Stage 2 reflects loss of compensatory reserve



A symptom-free person may have measurable metabolic disease.

The presymptomatic period is not a static state

- Stage 1 and stage 2 both represent autoimmune diabetes before symptoms.
- Stage 2 demonstrates worsening glucose regulation beyond stage 1.
- Progression is linked to a declining functional β -cell population.
- Classifying presymptomatic disease therefore requires both immunologic and metabolic information.



Stage 3: Clinical type 1 diabetes

Immunologic process

Islet-directed autoimmunity persists

Major β -cell loss is established

Metabolic state

Dysglycemia is clinically manifest

Insulin deficiency is severe

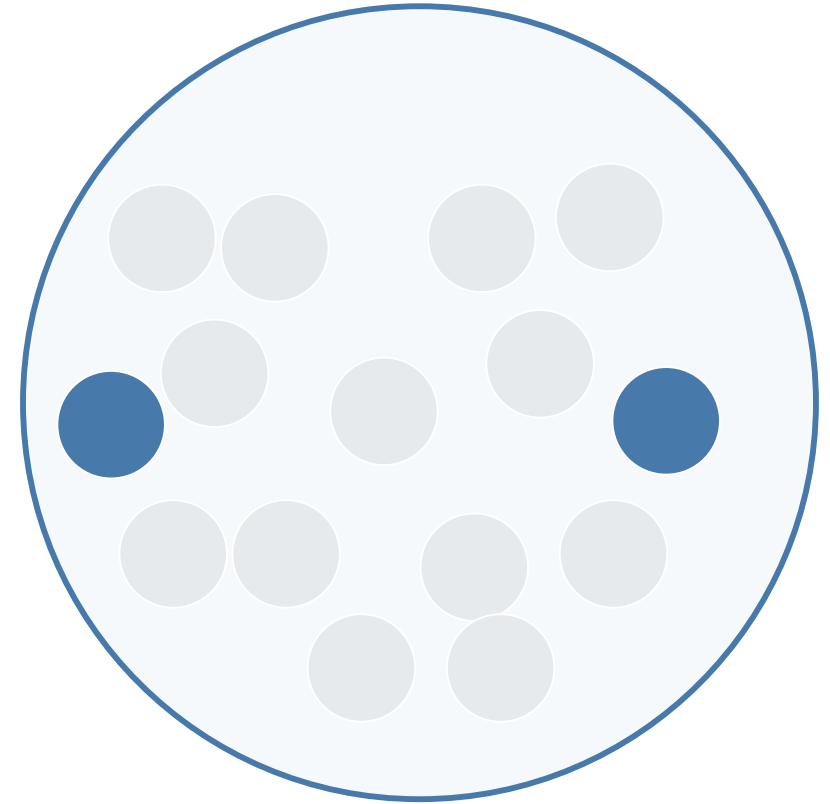
Manifestations

Polyuria, polydipsia, polyphagia

Ketoacidosis may occur

β -cell depletion underlies stage 3 disease

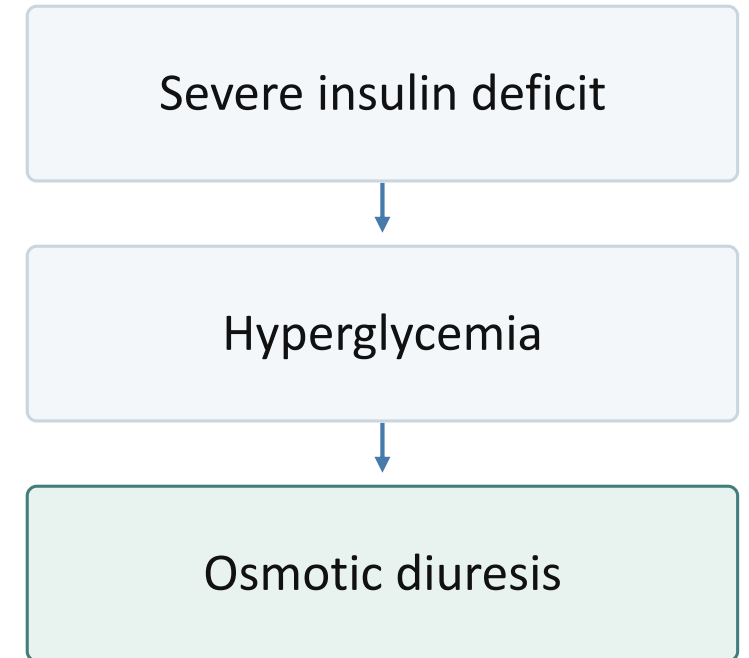
- Symptomatic disease typically after destruction of more than 90% of β cells.
- This is an approximate textbook statement, not an individual staging test.
- Large loss of cell number makes normal insulin production unsustainable.



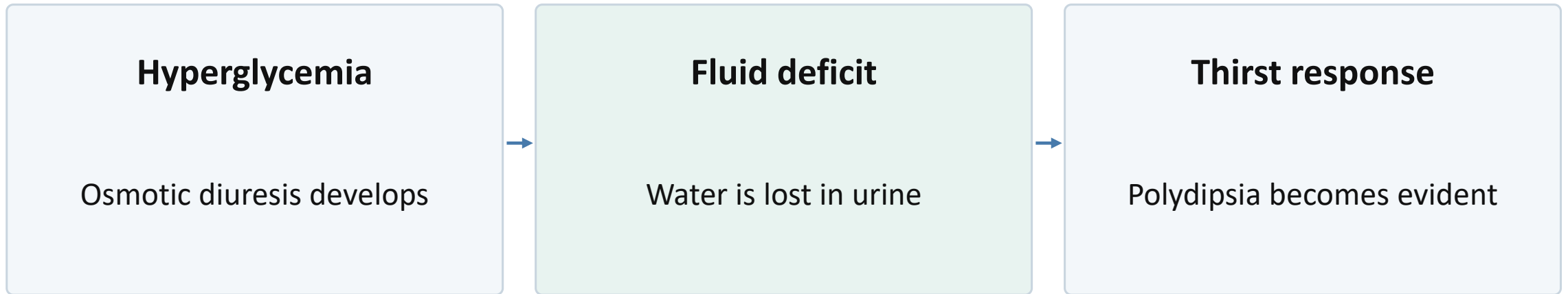
Schematic β -cell depletion; Cell counts are illustrative, not measured

Polyuria follows marked hyperglycemia

- Insufficient insulin leads to persistent elevation of plasma glucose.
- Hyperglycemia can cause glucose-associated osmotic diuresis.
- Increased urine volume is therefore a metabolic consequence of β -cell failure.
- Polyuria signals clinical decompensation rather than the start of autoimmunity.



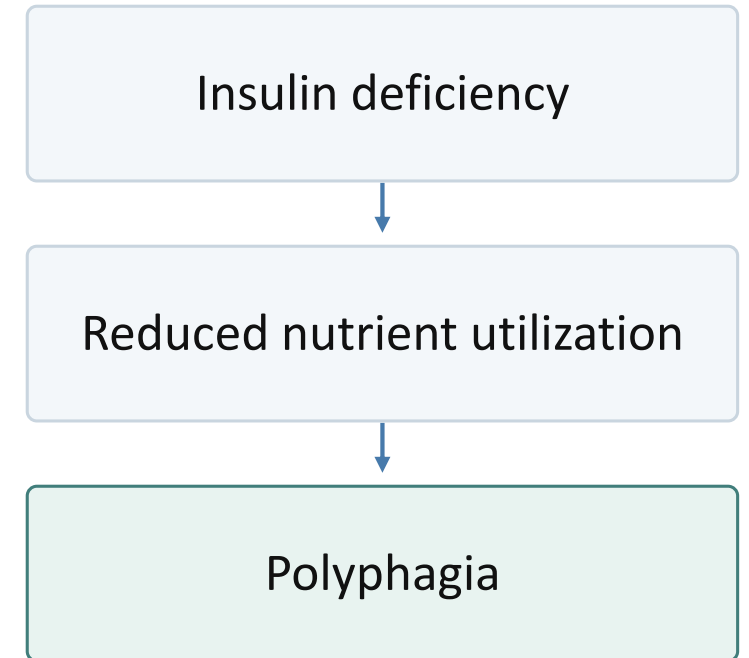
Polydipsia is secondary to fluid loss



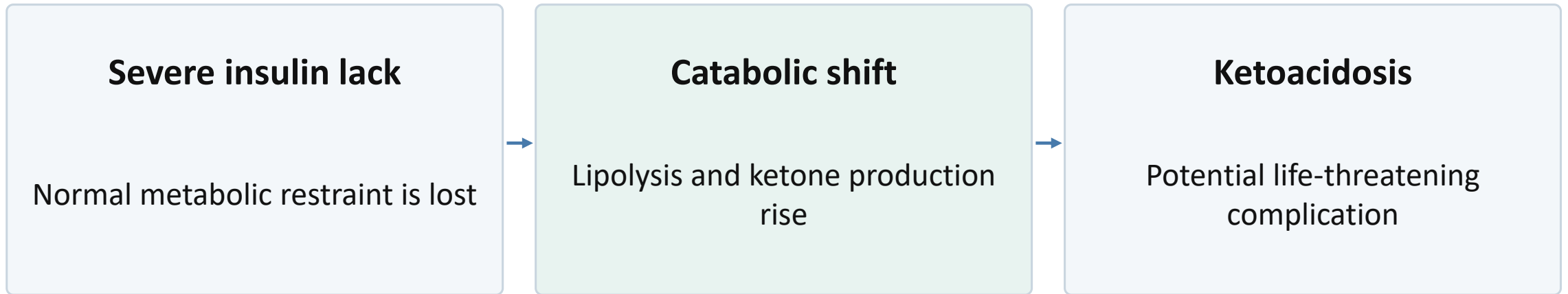
A clinical symptom can be traced to a specific failure of endocrine function.

Polyphagia accompanies an insulin-deficient state

- Glucose is abundant in blood but cannot be used normally by key insulin-responsive tissues.
- Anabolic actions of insulin are reduced.
- Disrupted nutrient utilization helps explain hunger despite hyperglycemia.
- This is a downstream metabolic effect—not a mechanism of autoimmune recognition.



Why ketoacidosis can develop



Autoimmune cell loss creates the endocrine deficit; Ketoacidosis is its consequence.

Five-year progression estimates in the source

Stage 1

Two or more islet autoantibodies

Normoglycemia

Less than 50% progress to symptomatic T1D in five years

Stage 2

Islet autoimmunity

Dysglycemia without symptoms

Approximately 75% progress in five years

Estimates as reported (2026); Not an individualized prediction.

Progression risk rises with dysglycemia

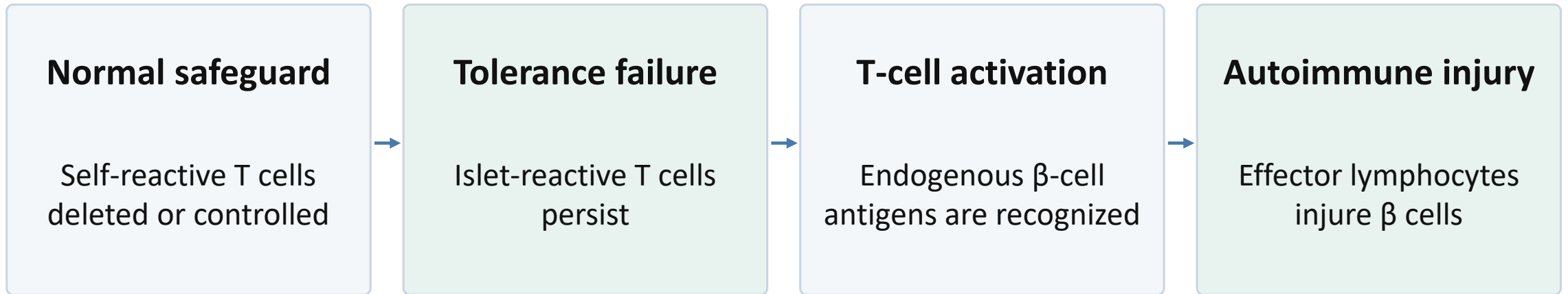
- The stage 2 estimate exceeds the stage 1 estimate in the Robbins account.
- Abnormal glucose handling indicates reduced reserve closer to clinical failure.
- The risk figures describe groups defined by disease stage.
- Do not infer an individual patient's exact time to presentation from stage alone.

Stage 1: <50% / 5y



Stage 2: 75% / 5y

T-cell self-tolerance is the decisive defect



Failure of self-tolerance is the central immune abnormality.

Two complementary layers of T-cell tolerance

Central tolerance

Deletion of autoreactive clones during thymic development

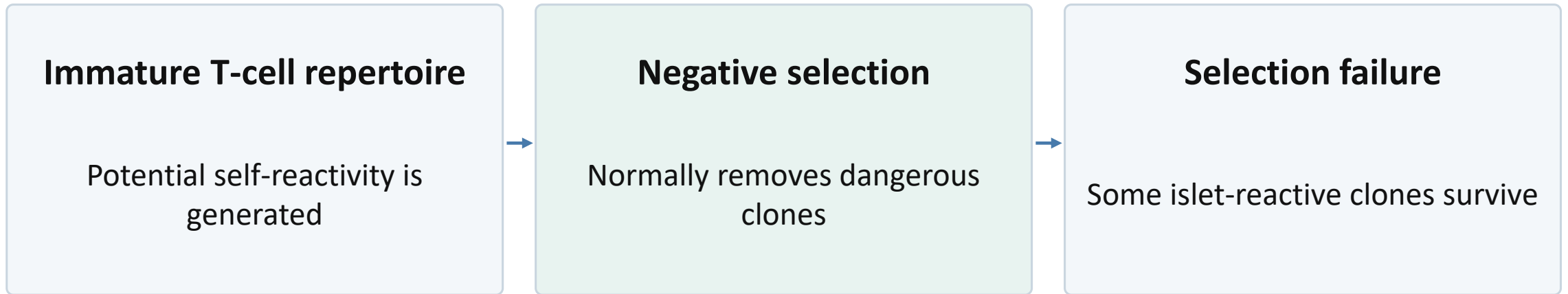
Insufficient deletion permits escape of self-reactive T cells

Peripheral tolerance

Regulatory mechanisms restrain escaped T cells

Defective regulation or suppression resistance enables immune attack

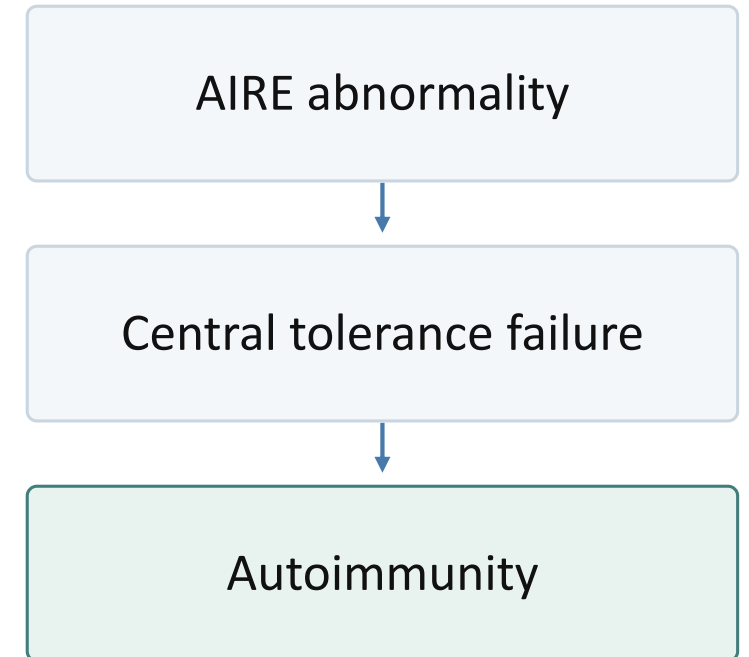
Defective thymic clonal deletion



The source presents defective deletion as one possible contributor, not as a proven universal defect.

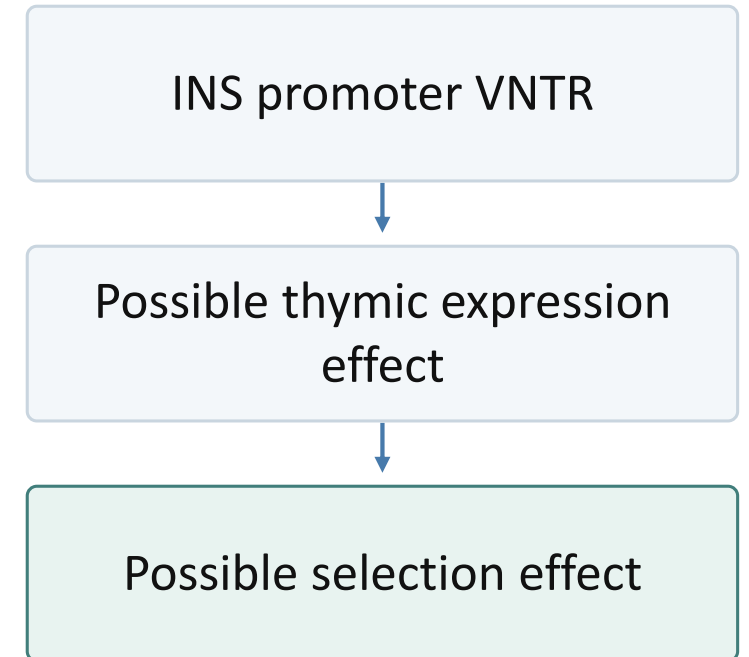
The AIRE association supports the tolerance model

- AIRE participates in central immune tolerance.
- Inherited defects of AIRE cause autoimmune polyendocrine syndrome type 1 (APS-1).
- Type 1 diabetes can occur in syndromes with profound immune-regulatory defects.
- This association supports—but does not reduce all type 1 diabetes to—one gene defect.

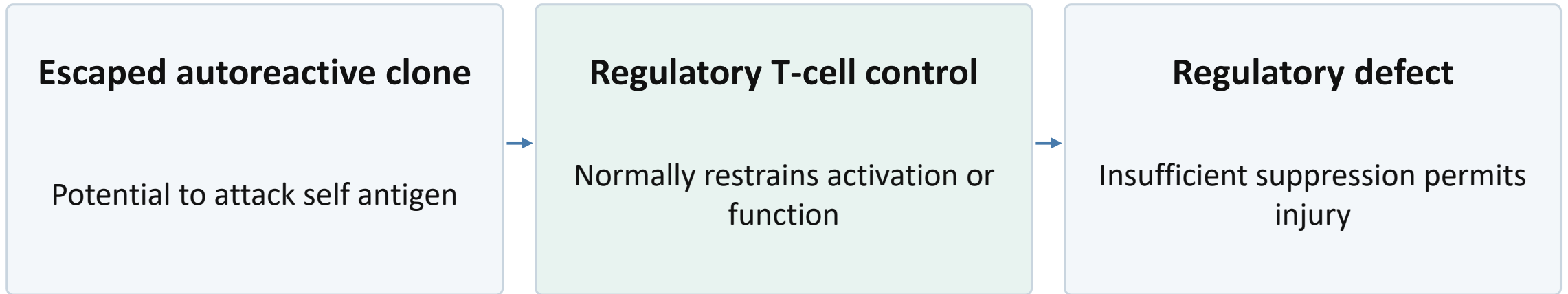


INS promoter variation is a susceptibility clue

- Variable number tandem repeats occur in the insulin gene promoter.
- The textbook proposes altered insulin expression in thymic antigen-presenting cells as a possibility.
- Such alteration might influence deletion of insulin-reactive T cells.
- The underlying mechanism of the genetic association is not established.



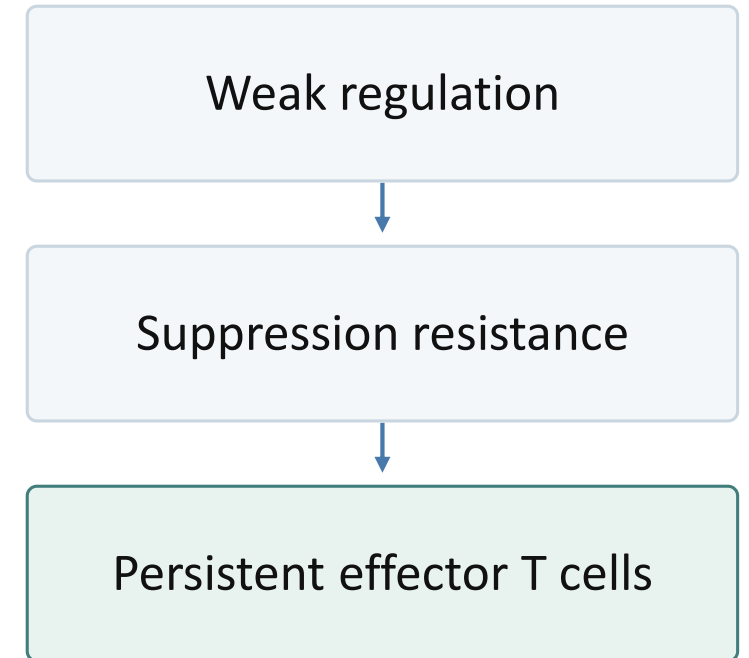
Regulatory T cells suppress effector responses



Peripheral regulation complements central deletion.

Effector cells can resist regulatory suppression

- Regulation may fail because regulatory T-cell function is defective.
- Alternatively, activated effector T cells may become abnormally resistant to suppression.
- Either failure can permit persistence of a destructive islet-directed response.
- The source presents these mechanisms as nonexclusive possibilities.



T-cell tolerance: Three mechanistic vulnerabilities

Thymic selection

Defective deletion of islet-reactive clones

Central escape

Treg effectiveness

Reduced suppressive function

Peripheral control failure

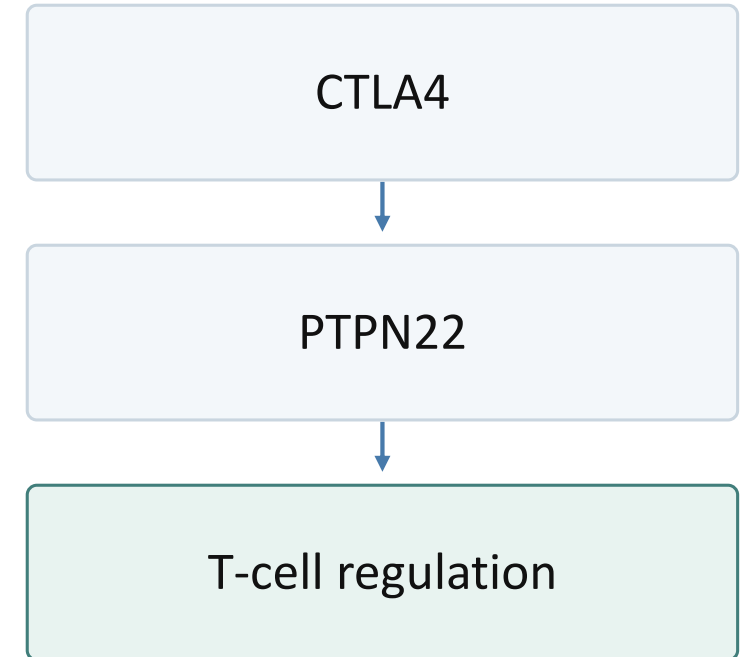
Effector responsiveness

Abnormal resistance to regulation

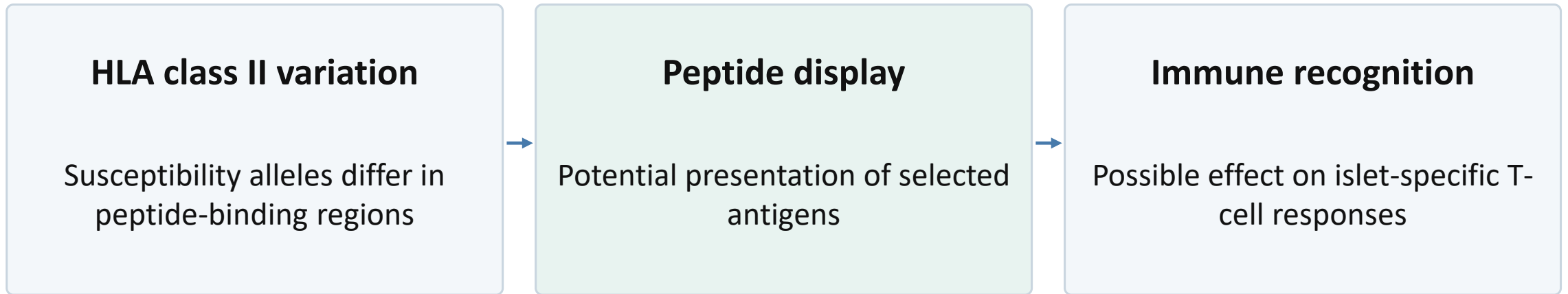
Continued autoreactivity

Genetic regulation intersects autoimmune susceptibility

- T1D has a strong genetic susceptibility component.
- CTLA4 and PTPN22 polymorphisms are linked to disease risk in the source.
- Both loci connect susceptibility with the regulation of T-cell responses.
- Genetic association by itself does not demonstrate a single causal pathway in an individual.



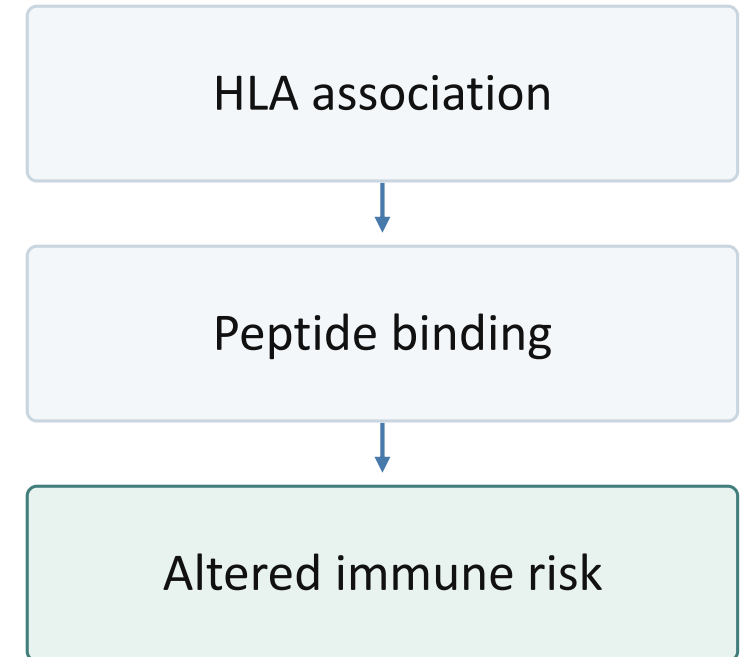
HLA variation implicates antigen presentation



The exact basis of susceptibility conferred by particular HLA alleles remains incompletely defined.

HLA is the leading inherited susceptibility locus

- The HLA gene cluster as the strongest T1D susceptibility locus.
- The textbook estimates a contribution as high as approximately half of genetic susceptibility.
- DR3/DR4 and certain DQ8-linked haplotypes are enriched in affected populations.
- These alleles alter risk; They are not sufficient for a diagnosis.



Genes create susceptibility, not certainty

Inherited factors

HLA class II loci

INS, CTLA4, PTPN22 and immune regulators

Different pathways can contribute to loss of tolerance

Non-genetic influences

Twin concordance is incomplete

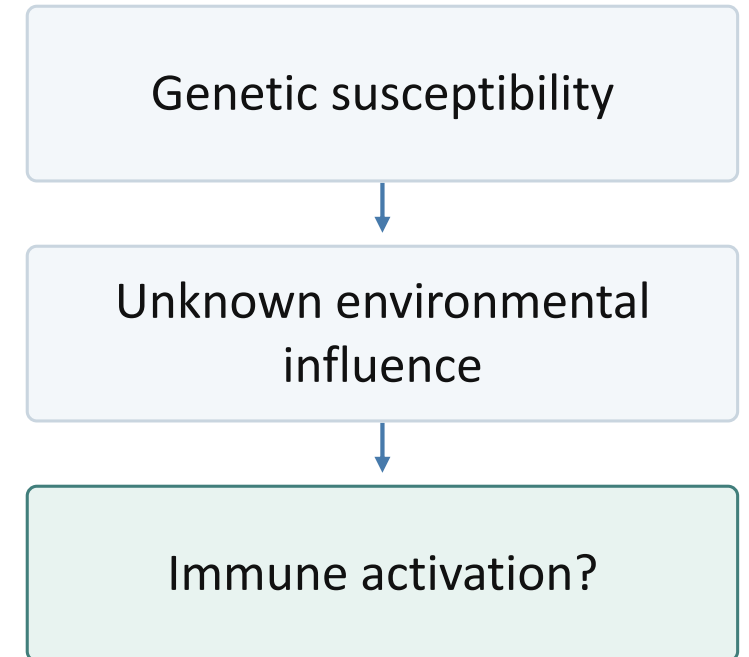
Potential environmental interactions

Triggers remain uncertain

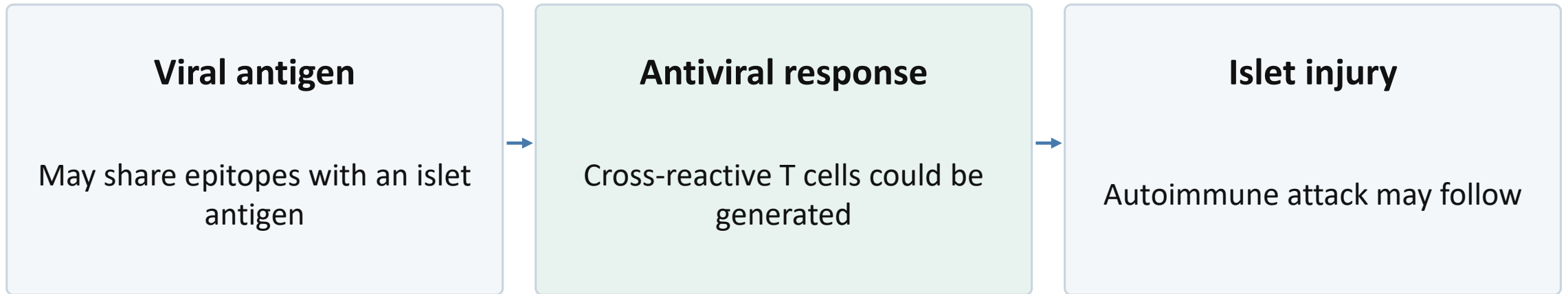
This is a multifactorial model, not single-gene determinism.

Environmental triggers remain unsettled

- The source notes incomplete concordance even among monozygotic twins.
- Viruses have been considered possible initiators of islet autoimmunity.
- Neither a specific causal virus nor a universal mechanism is established.
- Some infectious exposures have also been proposed to confer protection.

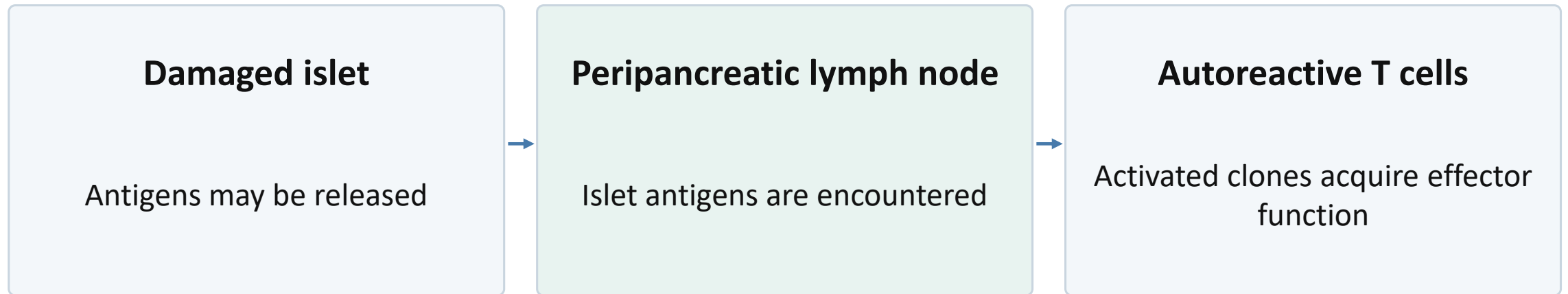


Molecular mimicry is a hypothesis



Conceptual possibility—not a confirmed obligatory trigger.

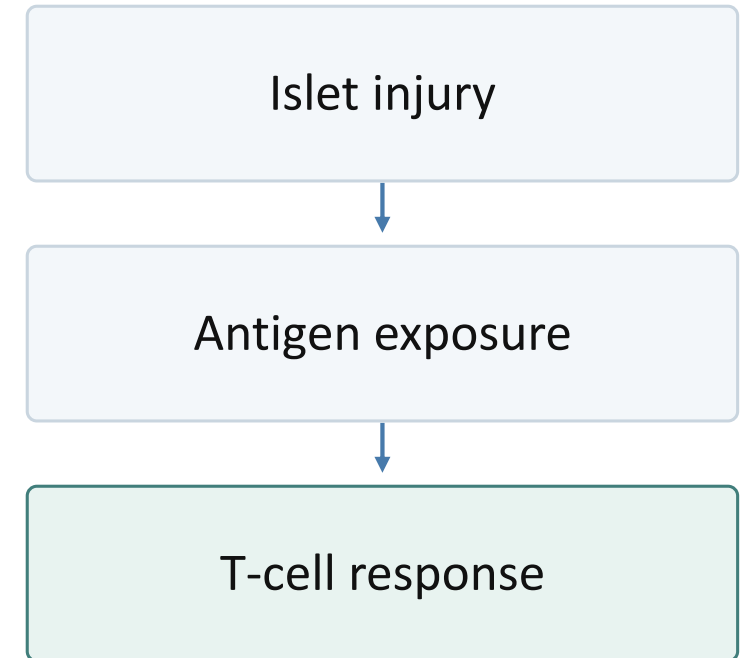
A proposed site of T-cell priming



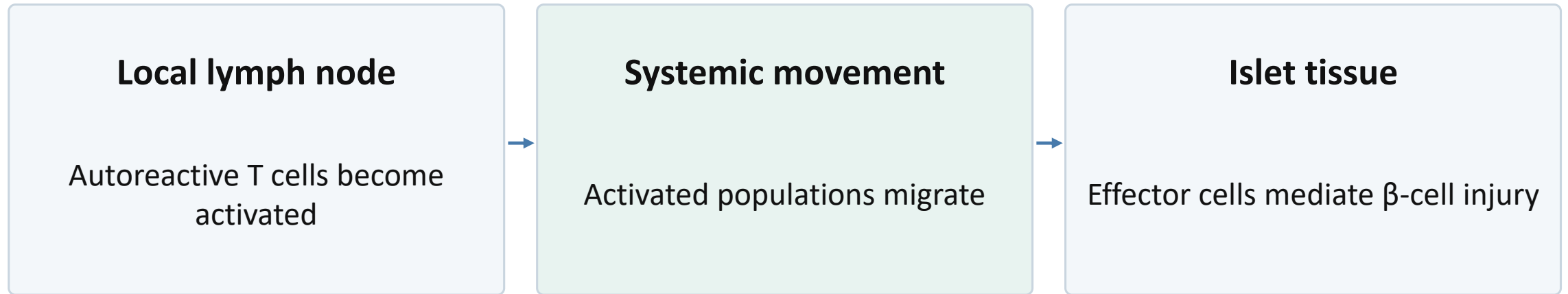
The site and initiating sequence are presented as proposed mechanisms, not direct observations.

Antigen release may amplify the immune process

- β -cell injury can expose endogenous islet components to immune recognition.
- The textbook proposes antigens from damaged islets as possible activating stimuli.
- T cells that escaped tolerance may respond when antigen is encountered.
- A reinforcing injury–antigen-exposure loop is a conceptual inference, not proven here.



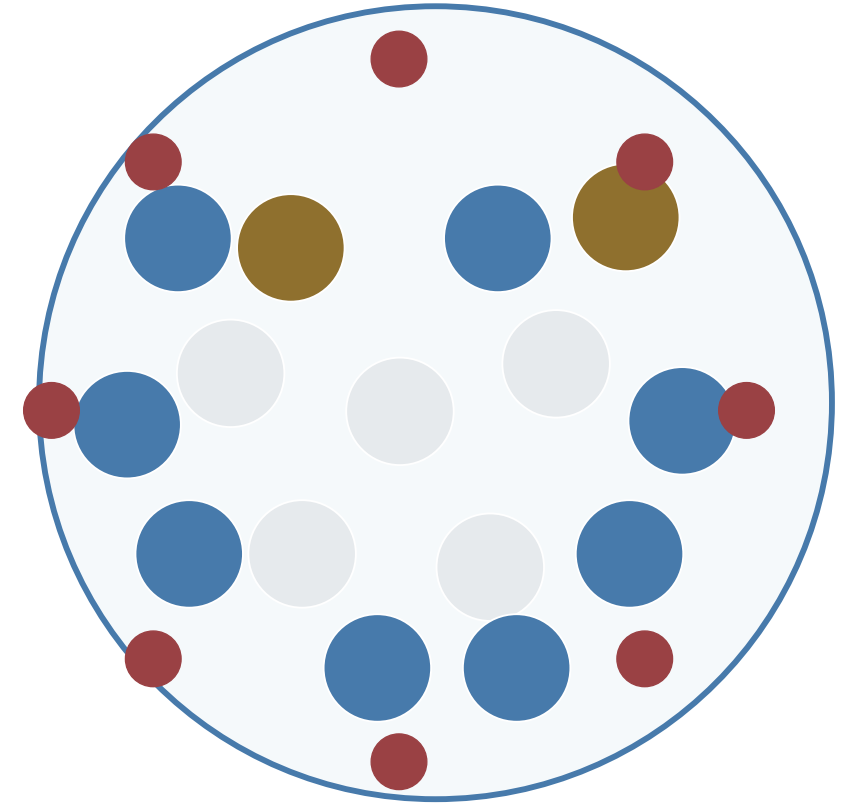
Activated effector T cells reach the pancreas



The pancreatic islet is the end-organ target of the activated immune response.

Insulitis: Inflammatory targeting of islets

- Insulitis is an inflammatory cell infiltrate involving pancreatic islets.
- T lymphocytes and macrophages among the cells found in T1D.
- Inflammation and selective β -cell depletion are characteristic pathologic findings.



Original schematic of islet-directed infiltration; Not a micrograph

Two T-cell effector populations injure β cells

CD8⁺ cytotoxic T cells

Directly kill β cells

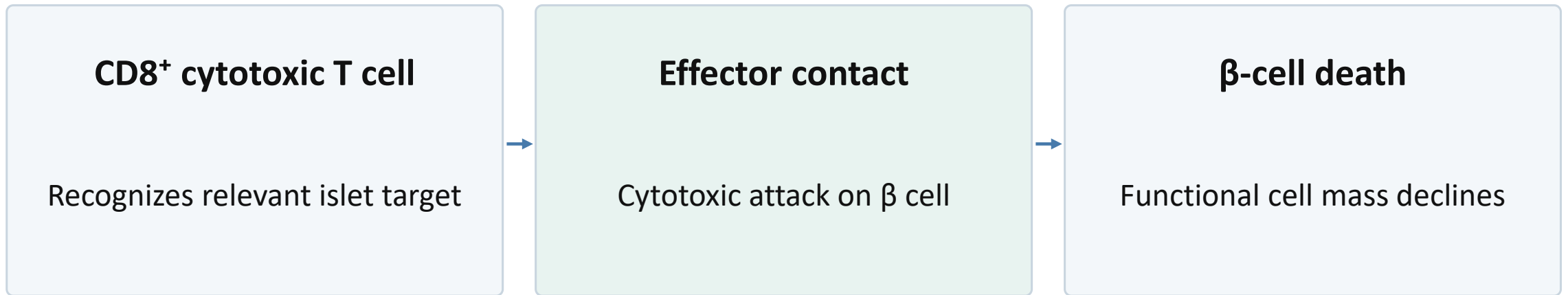
Cellular cytotoxicity is a principal destructive mechanism

Th1 helper T cells

Produce inflammatory cytokines

IFN- γ and TNF may contribute to β -cell injury

CD8⁺ cytotoxicity is a direct injury pathway



Robbins explicitly identifies CD8⁺ CTLs as direct β-cell killers.

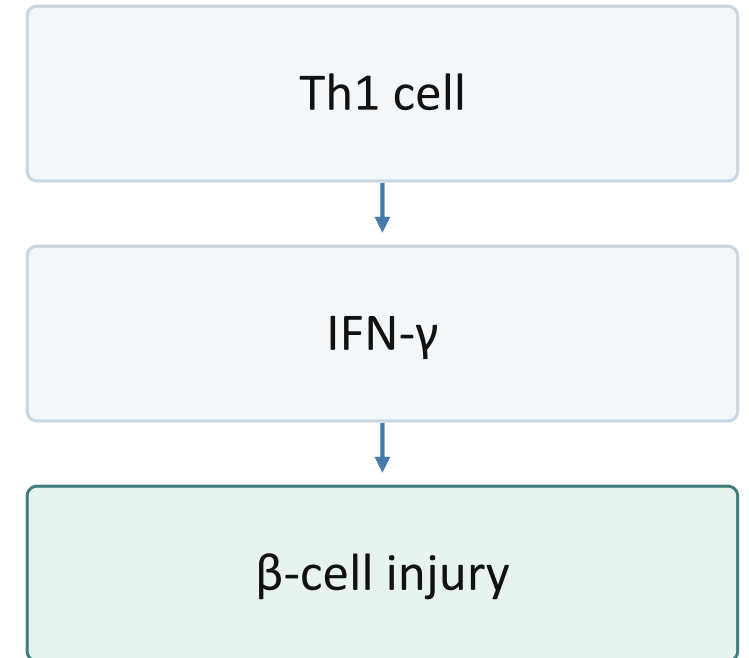
Th1-derived cytokines can injure β cells



Cytokine-mediated injury complements direct cytotoxicity.

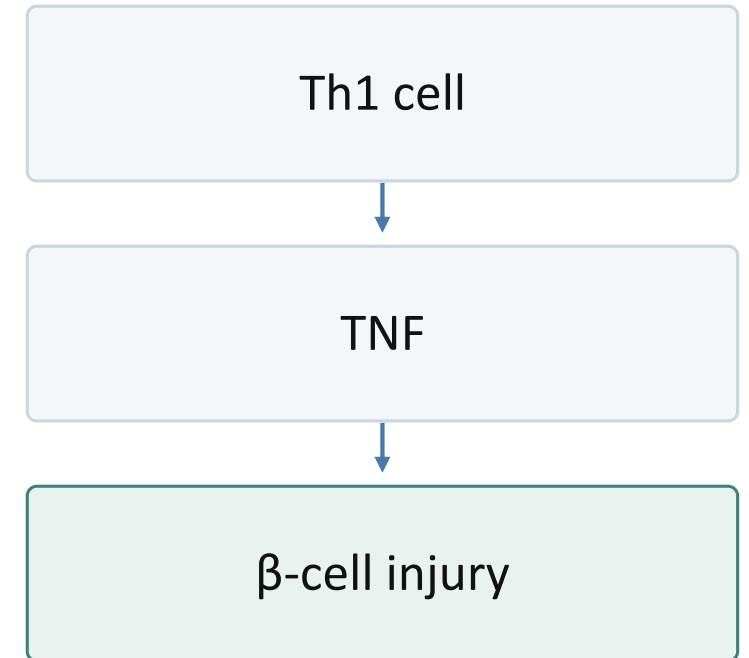
Interferon- γ belongs to the inflammatory pathway

- Interferon- γ (IFN- γ) among Th1-derived mediators.
- Its role in this account is immune-cell-associated β -cell injury.
- A named cytokine is not equivalent to a stand-alone diagnostic biomarker.
- The source does not provide a quantitative contribution of IFN- γ to cell loss.



Tumor necrosis factor is another injurious signal

- Tumor necrosis factor (TNF) is included among the relevant Th1 cytokines.
- Inflammatory mediators can coexist with direct CD8⁺ cytotoxic killing.
- Different pathways may operate concurrently within an affected islet.
- The textbook does not establish a fixed hierarchy between TNF and IFN- γ .



Direct killing versus cytokine-associated injury

Contact-dependent route

CD8⁺ cytotoxic T cells

Direct killing of β cells

Immune-effector cellular pathway

Inflammatory route

Th1 T cells

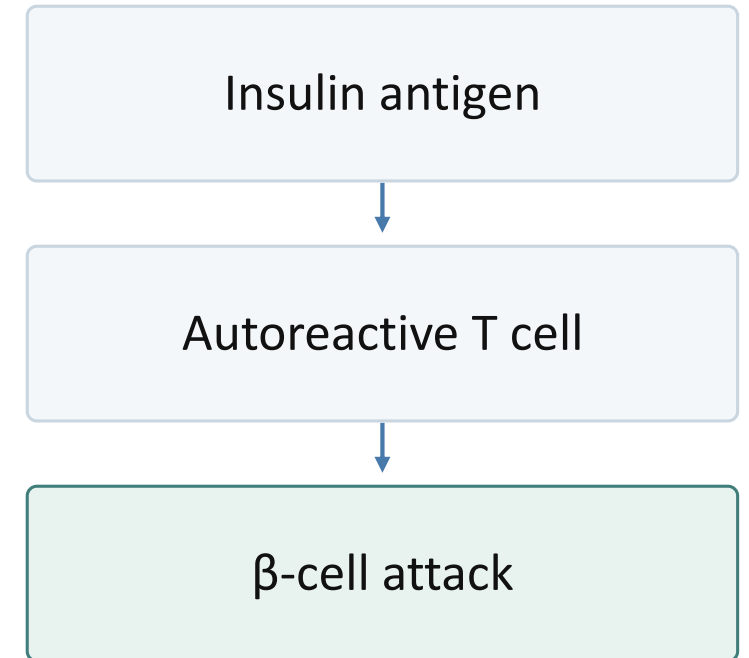
IFN- γ and TNF release

Contributes to β -cell injury

Both pathways are derived from the Robbins mechanism section.

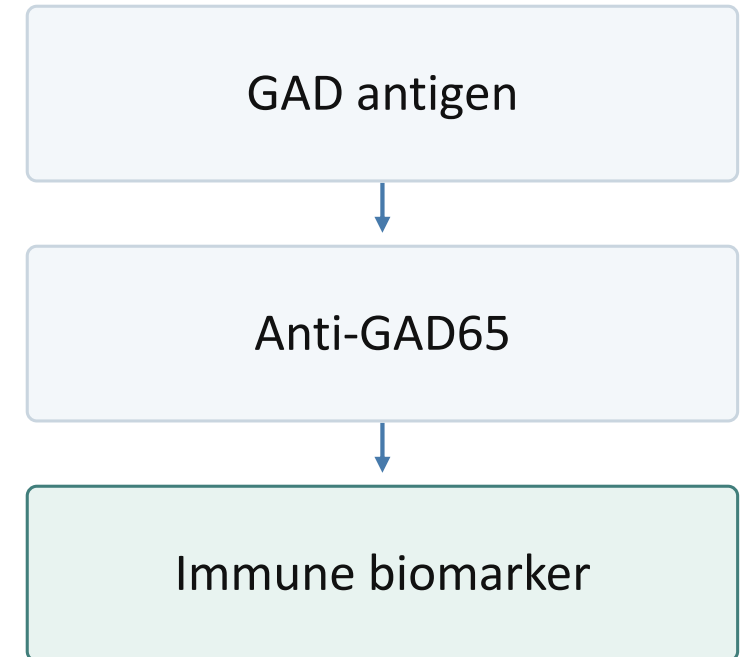
Insulin is itself an islet autoantigen

- Insulin is one antigen considered a target of autoimmune recognition.
- Its production by β cells creates antigenic specificity for the endocrine target.
- Insulin-related genetic susceptibility may intersect with thymic tolerance.
- Autoantigen recognition and direct tissue injury are separate mechanistic steps.



Glutamic acid decarboxylase is an autoantigen

- The β -cell enzyme glutamic acid decarboxylase (GAD) is another antigenic target.
- Anti-GAD65 autoantibodies are listed among circulating T1D-associated autoantibodies.
- Antigen specificity explains why an islet-focused autoimmune phenotype is recognizable.
- Antibody detection does not by itself establish antibody-mediated killing.



Common islet autoantibodies in the source

Marker	Antigen or label	Interpretation
Anti-GAD65	Glutamic acid decarboxylase	Marker of islet autoimmunity
Anti-IA2	IA2-associated antigen	Marker of islet autoimmunity
Anti-ZnT8	Zinc transporter 8	Marker of islet autoimmunity

Names are drawn from the Robbins comparison table; Test performance is not specified.

Why the role of antibodies remains unresolved

What is demonstrated

Most patients may have circulating islet autoantibodies

Antibodies can precede clinical onset

Useful evidence of immune activation

What is not established

Direct antibody-driven β -cell destruction

That every positive antibody causes cell injury

That antibodies alone determine disease stage

The source explicitly distinguishes association from proven pathogenicity.

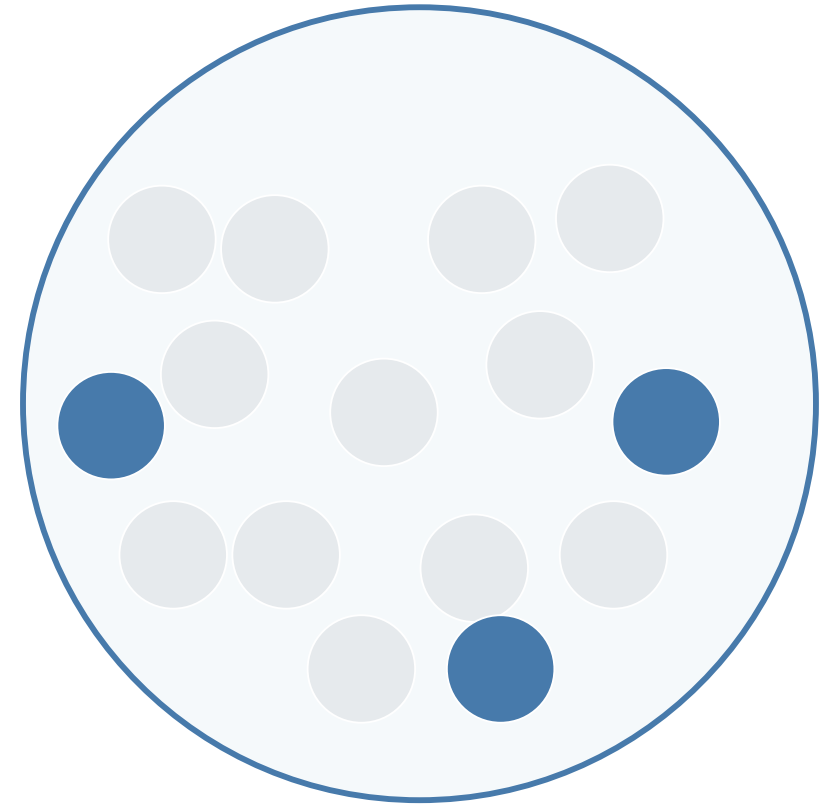
Checkpoint blockade illustrates the role of restraint



A clinical perturbation of tolerance supports the mechanistic model.

β -cell depletion alters islet composition

- The type 1 diabetes comparison table describes β -cell depletion and islet atrophy.
- Other endocrine cell types may remain within the depleted endocrine structures.
- A schematic can explain selective loss but cannot establish microscopic diagnosis.



Original illustrative islet composition, not authentic tissue

Morphology helps distinguish diabetic mechanisms

Type 1 diabetes

T cells and macrophages may infiltrate islets

Insulitis is characteristic

β -cell depletion and islet atrophy

Type 2 diabetes

No autoimmune islet-destruction mechanism established

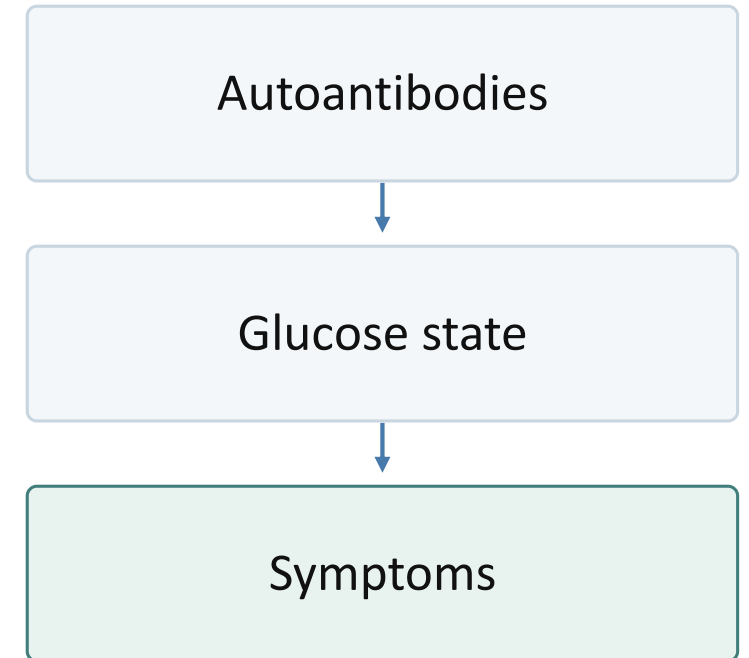
Islet amyloid is described

β -cell depletion usually milder

Patterns summarize Robbins; Neither column is a stand-alone diagnostic algorithm.

Histology is not a routine staging surrogate

- The three stages are defined using autoimmunity, glycemic status and symptoms.
- They are not defined by direct pancreatic biopsies or β -cell counts.
- Functional reserve is inferred from clinical and metabolic behavior.
- Islet lesions explain biology but should not be confused with stage-defining tests.



Slow progression is compatible with autoimmune disease

Typical course

Long presymptomatic phase

Symptoms may appear abruptly after major loss of reserve

LADA

Adult presentation with islet autoantibodies

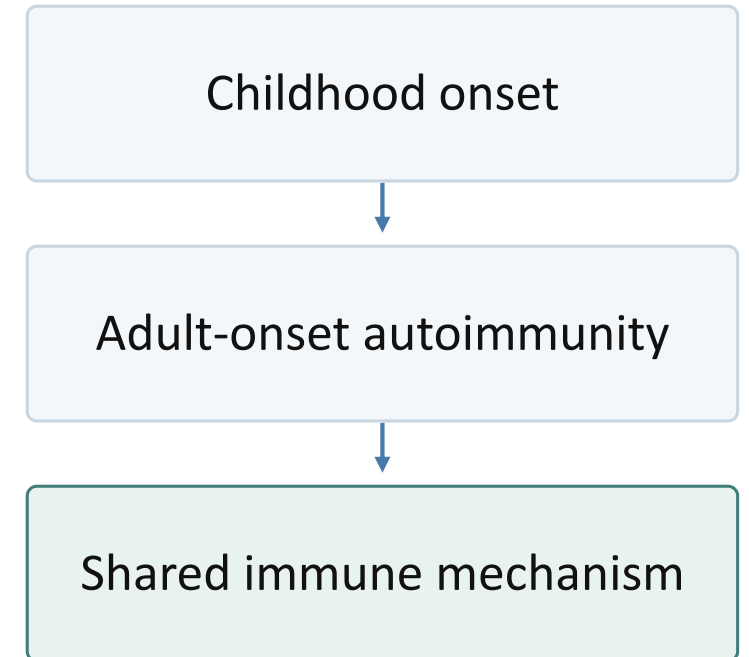
Slower progression

Insulin may not be needed immediately

LADA is discussed in the parent Type 1 Diabetes section.

Type 1 diabetes is not restricted to childhood

- The source emphasizes that type 1 diabetes can develop at any age.
- The term juvenile-onset diabetes is therefore not preferred.
- Insulin dependence describes treatment need, not an exclusive pathologic category.
- Immune-pathogenesis evidence is more informative than age alone.



Case study: Autoimmunity before hyperglycemia

A person being monitored because of familial susceptibility has two distinct islet autoantibodies on repeat testing. Glucose regulation remains normal, and no symptoms are present.

This is a fictional educational scenario; No patient data are represented.

What is the correct stage?

Stage 1: Multiple autoantibodies, normoglycemia, no symptoms.

Case study: Silent metabolic progression

An individual with established islet autoimmunity develops abnormal glucose tolerance but reports no polyuria, thirst or other classic symptoms.

The aim is to classify biological stage independently of symptom burden.

Which finding defines progression?

Stage 2: Dysglycemia despite absence of symptoms.

Case study: Symptomatic β -cell insufficiency

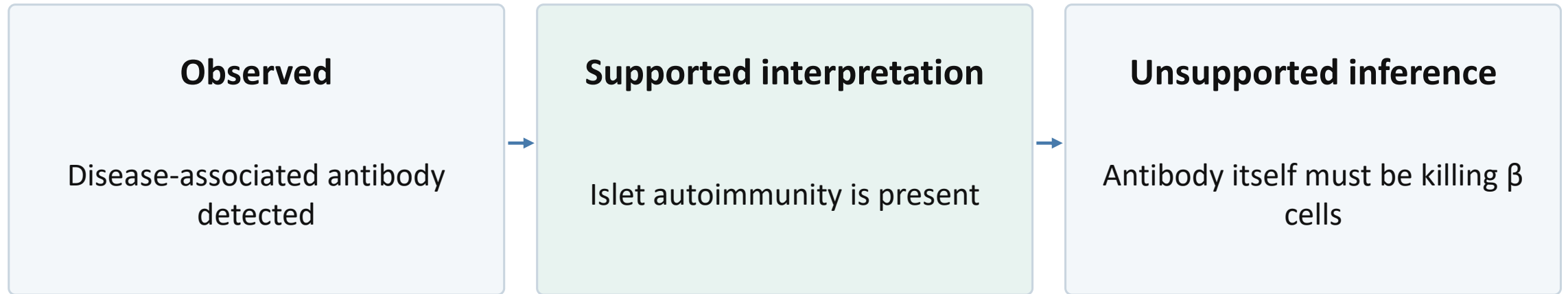
A patient presents with polyuria, polydipsia and marked hyperglycemia. Prior tests documented multiple islet autoantibodies. An insulin-deficient phenotype has now become clinically apparent.

This scenario intentionally omits invented numerical laboratory values.

What is the stage?

Stage 3: Dysglycemia with clinical symptoms.

When interpreting autoantibodies, avoid a causal leap



Biomarkers and effectors occupy different positions in a causal model.

T1D versus T2D: Mechanistic discrimination

Question	Autoimmune T1D	Typical T2D
Primary mechanism	Immune effector destruction	Insulin resistance plus inadequate compensation
Islet antibodies	Commonly present	Typically absent
Islet lesion	Insulitis, β -cell depletion	Amyloid, relatively mild β -cell loss
Role of HLA	Strong susceptibility association	No analogous HLA linkage reported

Evidence, proposals, and unknowns

Established in the source

T-cell self-tolerance failure

CD8⁺ cytotoxicity and Th1 injury

Progressive β -cell depletion

Proposed / unresolved

Exact initiating antigenic event

Specific environmental trigger

Whether autoantibodies directly injure β cells

The categories describe certainty conveyed by the textbook, not an exhaustive literature review.

Integrating the pathogenesis



One causal narrative connects inherited risk, tissue injury and phenotype.

Three conclusions for pathology practice

Mechanistic

Type 1 diabetes is predominantly a T-cell-mediated autoimmune disorder

Antibody pathogenicity remains unresolved

Temporal

Autoimmunity precedes overt hyperglycemia

Stage 1 → stage 2 → stage 3 describes clinical evolution

Morphologic

Insulitis involves inflammatory islet infiltration

β -cell depletion underlies insulin deficiency

Principal textbook and source context

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026), Chapter 24 — The Endocrine System

Primary topic: Mechanisms of β -Cell Destruction (printed pp. 1002–1003)

Context: Pathogenesis of Type 1 Diabetes and adjacent endocrine pancreas sections (pp. 997–1003)

Staging concept in textbook Fig. 24.31 is credited to Insel RA et al., *Diabetes Care* (2015); diagrams here are newly authored schematics.