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ENDOCRINOLOGY

Type 1 diabetes mellitus

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T1DM is a chronic, progressive, autoimmune disorder with incomplete penetrance (estimated as 40–70% from monozygotic twin studies). In individuals with a genetic susceptibility to T1DM, an abnormal, unregulated, autoimmune response targeting β cells can develop, which leads to progressive islet damage and insulin insufficiency. The environmental triggers that interact with susceptibility and resistance genes to initiate and perpetuate the disease remain to be defined.

The incidence of T1DM in developed countries is 10–60 cases per 100,000 people, and is increasing by ~4% per year. Improved understanding of disease-relevant immunological pathways has led to new intervention strategies, several of which are in clinical development. These offer some hope that β-cell destruction can be halted and immunological tolerance restored in patients with T1DM, although many challenges undoubtedly lie ahead.

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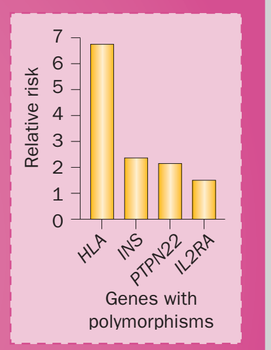
Risk factors for T1DM

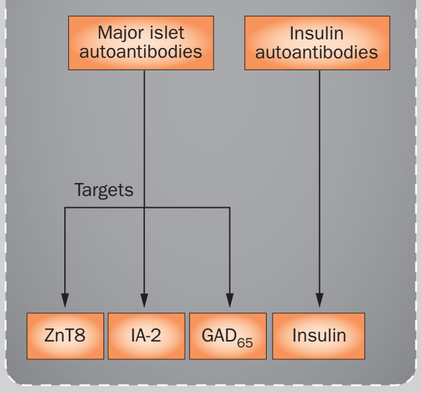
- Genetic risk of T1DM is conferred by polymorphisms in numerous genes that regulate innate and adaptive immunity, β-cell function and apoptosis rate. These polymorphisms modulate immune responses at various stages of disease progression and influence the ability of β cells to endure or escape the autoimmune process. An individual's HLA haplotype accounts for >50% of their genetic risk of T1DM, but over 50 non-HLA loci also contribute to disease susceptibility. For example, disease-associated polymorphisms in *INS*, the preproinsulin gene, are thought to reduce thymic expression of proinsulin, which shifts the balance of peripheral T cells recognizing this key autoantigen from a predominantly T_{REG} to a predominantly effector T-cell population. Other genes influence innate responsiveness to inflammation (e.g. *IFIH1*) and regulation of immune responses (*IL2RA*, *IL2*, *PTPN22*).
- Rare syndromes associated with T1DM include APS1, caused by loss-of-function mutations in *AIRE* that abrogate expression of insulin in the thymus, and IPEX, caused by mutations in *FOXP3* that lead to loss of T_{REG} cells.
- Several putative nongenetic factors also influence the risk of T1DM: breastfeeding may be protective, whereas viral infection, vitamin D deficiency, Caesarean section and low birth weight may increase risk. Notably, early life events seem to be important determinants of gene–environment interactions leading to T1DM.

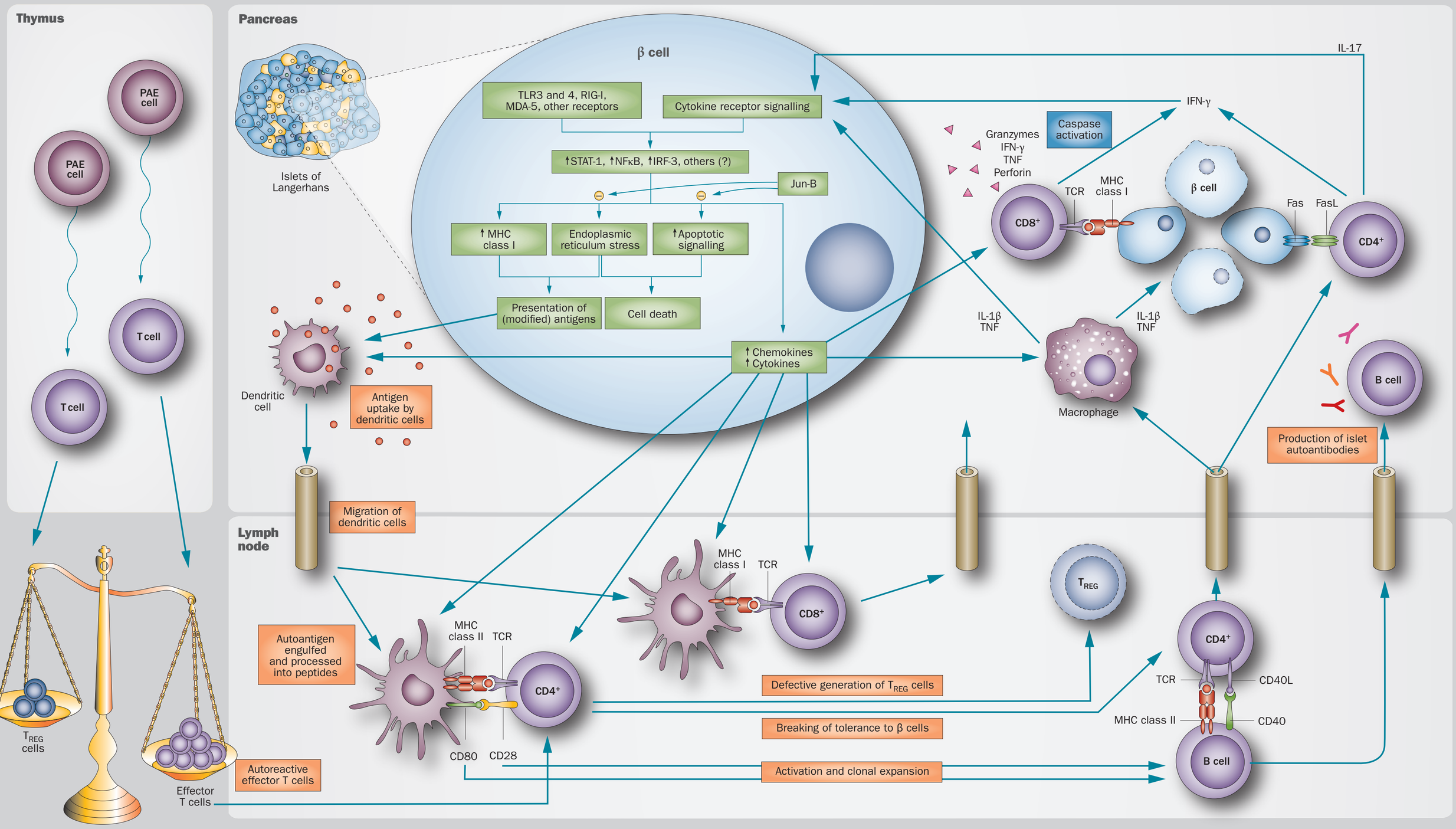


Development of T1DM

- Early islet inflammation probably involves activation of innate immunity and crosstalk between immune cells and pancreatic β cells. Cytokines and chemokines released by both cell types, as well as 'danger signals' provided by dying β cells, activate and attract immune cells to pancreatic islets (a process termed insulitis), which eventually escalates to a full-blown autoimmune assault.
- Once islet autoimmunity is triggered, which is potentially marked by the initial appearance of islet cell autoantibodies, multiple β-cell autoantigens are progressively targeted.
- Killing of β cells probably results from multiple mechanisms, most notably recruitment of cytotoxic $CD8^+$ T cells and indirect, cytokine-mediated upregulation of β-cell apoptosis.
- Loss of β cells within the pancreas is lobular and asynchronous, such that healthy islets coexist with islets infiltrated by T cells and islets in which all β cells have been destroyed. Furthermore, in children monitored from birth until the development of T1DM, levels of autoantibodies fluctuate independently. These observations imply heterogeneity in the timing and intensity of autoimmunity during the prodrome of T1DM. However, high titres of insulin autoantibodies and the presence of multiple autoantibody specificities correlate with an increased rate of disease progression.

Children who express >2 autoantibodies reacting with insulin, GAD_{65}, IA-2 and/or ZnT8 will in 80–90% of cases progress to T1DM, although in some individuals this process can take more than a decade.





Epidemiology of T1DM

The incidence of T1DM varies from <5 cases per 100,000 people in developing countries to >60 cases per 100,000 people in Finland. Incidence is increasing in most countries where data are being collected, especially in children under 5 years of age. This trend probably reflects changing environmental influences rather than changes in the gene pool.

The stages of β-cell loss and timing of prevention strategies

Note that the colours used in this graph correspond to the box colours throughout the poster.

Remaining questions for future studies

- Which environmental factors trigger insulitis and T1DM?
- How do these environmental factors interact with T1DM resistance and susceptibility genes?
- Which polymorphisms in susceptibility loci cause T1DM?
- What are the functional roles of candidate resistance and susceptibility genes for T1DM?
- Which are the major effector mechanisms of β-cell death in T1DM?
- Are these mechanisms modulated by the genetic background of affected individuals?
- Can insulitis be resolved? If yes, what are the steps and regulatory mechanisms involved in termination of the inflammatory response and restoration of islet homeostasis?
- Will combinations of immunotherapies that target different disease pathways have synergistic effects on T1DM?

Abbreviations

APS1	autoimmune polyendocrinopathy candidiasis ectodermal dystrophy
IA-2	islet-associated tyrosine phosphatase
IPEX	immunodeficiency polyendocrinopathy, enteropathy, X-linked syndrome
Fas	apoptosis-mediating surface antigen FAS
FasL	Fas antigen ligand
GAD_{65}	glutamic acid decarboxylase-65
IFN	interferon
IRF-3	interferon regulatory factor 3
Jun-B	transcription factor Jun-B
MDA-5	melanoma differentiation-associated protein 5
NFκB	nuclear factor κB
PAE	peripheral antigen expressing
RIG-I	retinoic acid-inducible gene-I
STAT-1	signal transducer, activator of transcription-α/β
TCR	T-cell receptor
T1DM	type 1 diabetes mellitus
T_H1	T-helper-1 cell
TLR	Toll-like receptor
TNF	tumour necrosis factor
T_{REG}	T-regulatory cell
ZnT8	zinc transporter 8

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