open.michigan

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Objectives

The objectives of this lecture are to understand:

1. The Pathogenesis of Autoimmune Diabetes (Type 1A diabetes)
2. The role of T cells in Disease Pathogenesis
3. The role of Cytokines in Disease Pathogenesis
4. The role of Islet Autoantibodies

Diabetes Mellitus

A systemic disease with multiple metabolic abnormalities, chief among which is an elevation in plasma glucose.

In addition to the primary defect in carbohydrate metabolism defects in lipid metabolism are widespread, with elevations in plasma FFA and TG, and, in some circumstances, of ketones.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

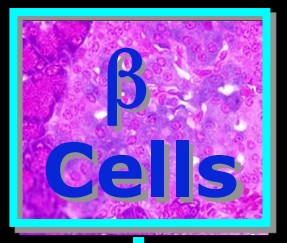
Gavin JR et al. Diabetes Care*, 20:1183-1197, 1997*

I. Type 1 diabetes
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes

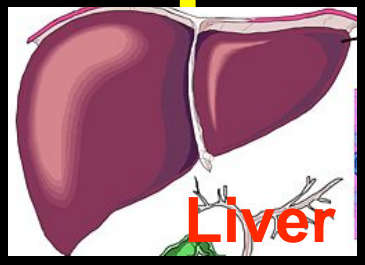
III. Other specific types

Regulation of Plasma Glucose

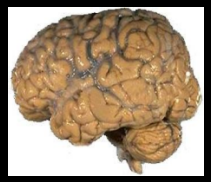


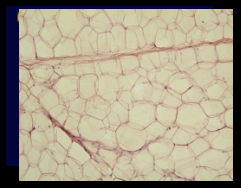
Steady State
Plasma Glucose

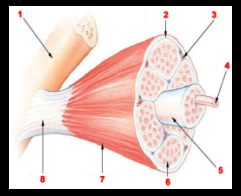
Glucose Production



Glucose Disposal





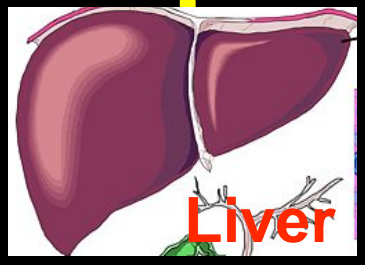


Peripheral Tissues

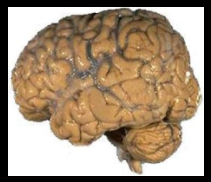
Regulation of Plasma Glucose

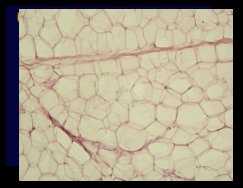
Steady State
Plasma Glucose

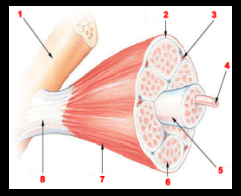
Glucose Production



Glucose Disposal







Peripheral Tissues

Diabetes Mellitus- Type 1

Increased thirst (polydypsia)

Increased urination (polyuria)

Increased appetite (polyphagia)

Weight loss

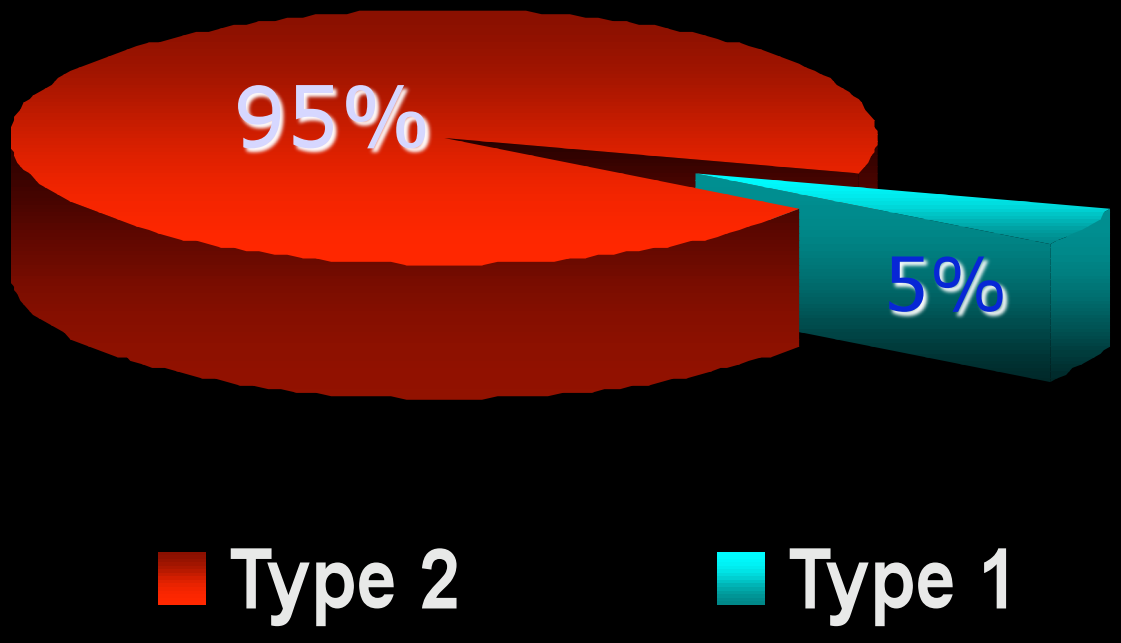
Fatigue

Rapid, early onset (before age 15)

Differences Between Type 1 and Type 2 Diabetes

	Type 1	Type 2
Age of onset	Young	Older
Type of onset	Acute	Insidious
Genetic background	HLA related	Not HLA related
Islet cell antibodies	Yes	No
Insulin secretion	Absent	Present
Nutritional status	Thin	Obese
Insulin dependence	Yes	No
Insulin resistance	No	Yes
Responsiveness to Orals	No	Yes
Ketosis proneness	Yes	No

Relative Proportions of Types 1 & 2 DM



Type 1 diabetes (IDDM)

Chronic autoimmune disease with juvenile onset, but may develop in adults as well as elderly (LADA).

Polygenic disease

- Strong MHC linkage
- Non-MHC genes

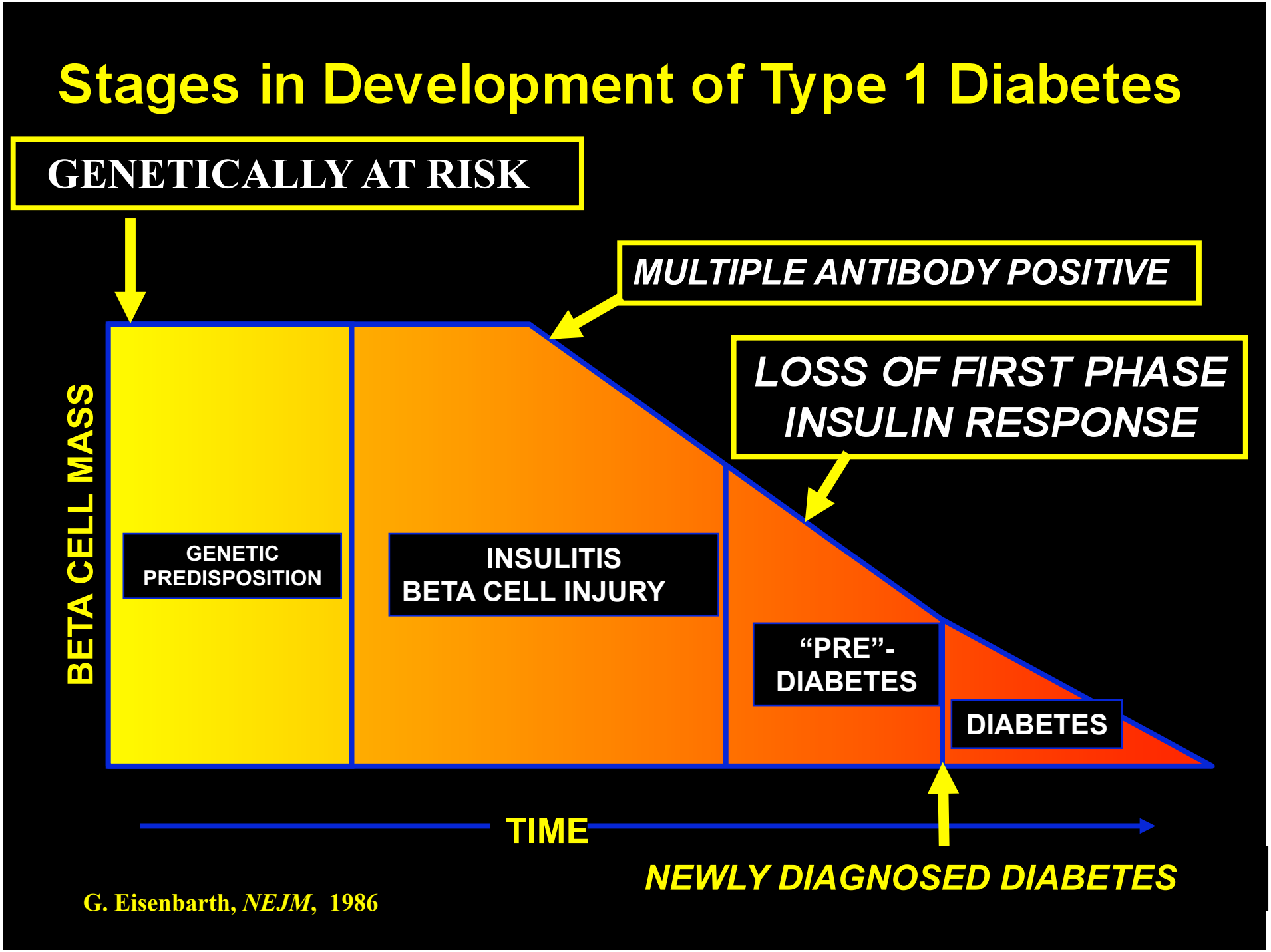
Autoimmune etiology

- Antibodies to islet autoantigens
- Autoreactive T cells

Immune-modulation alters the course of disease

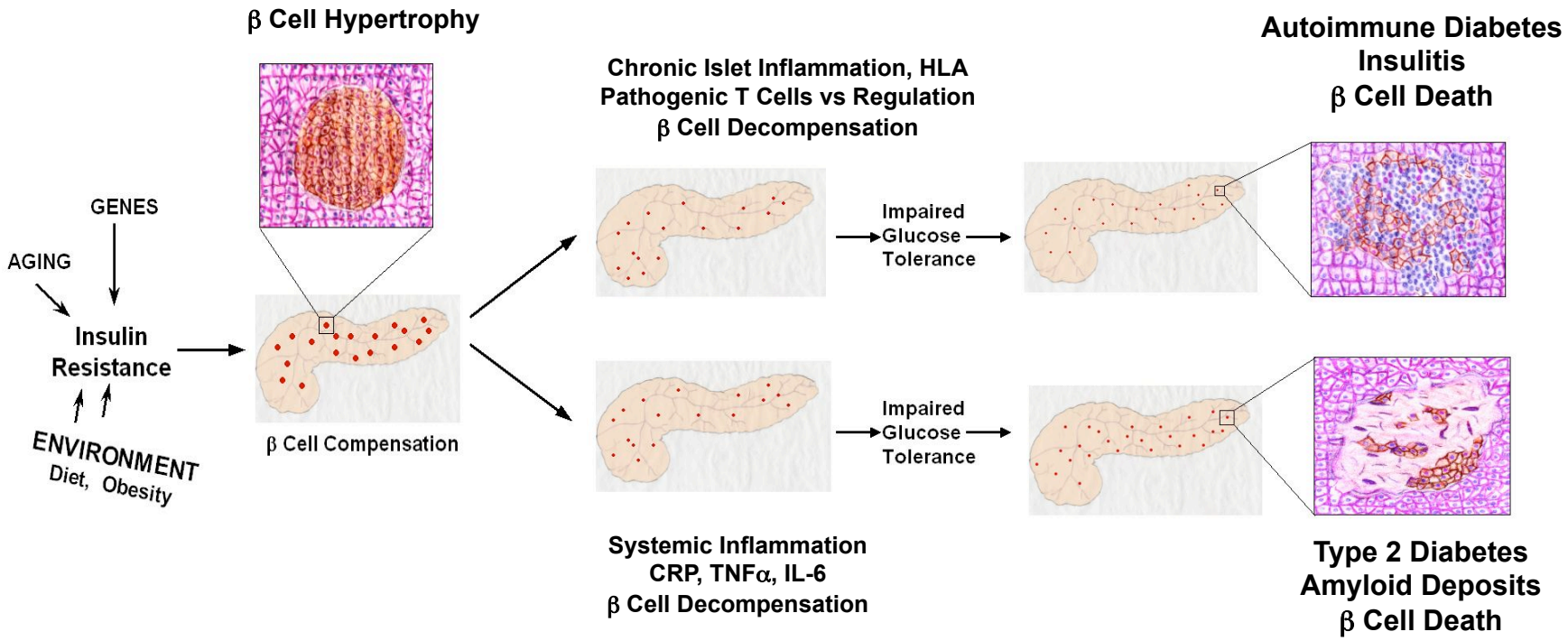
- Antigen vaccination
- General immunosuppression

Stages in Development of Type 1 Diabetes



G. Eisenbarth, *NEJM*, 1986

Type 1 diabetes: a chronic inflammatory disease of the islets



Pietropaolo M et al. *Diabetes* 56:1189-97, 2007

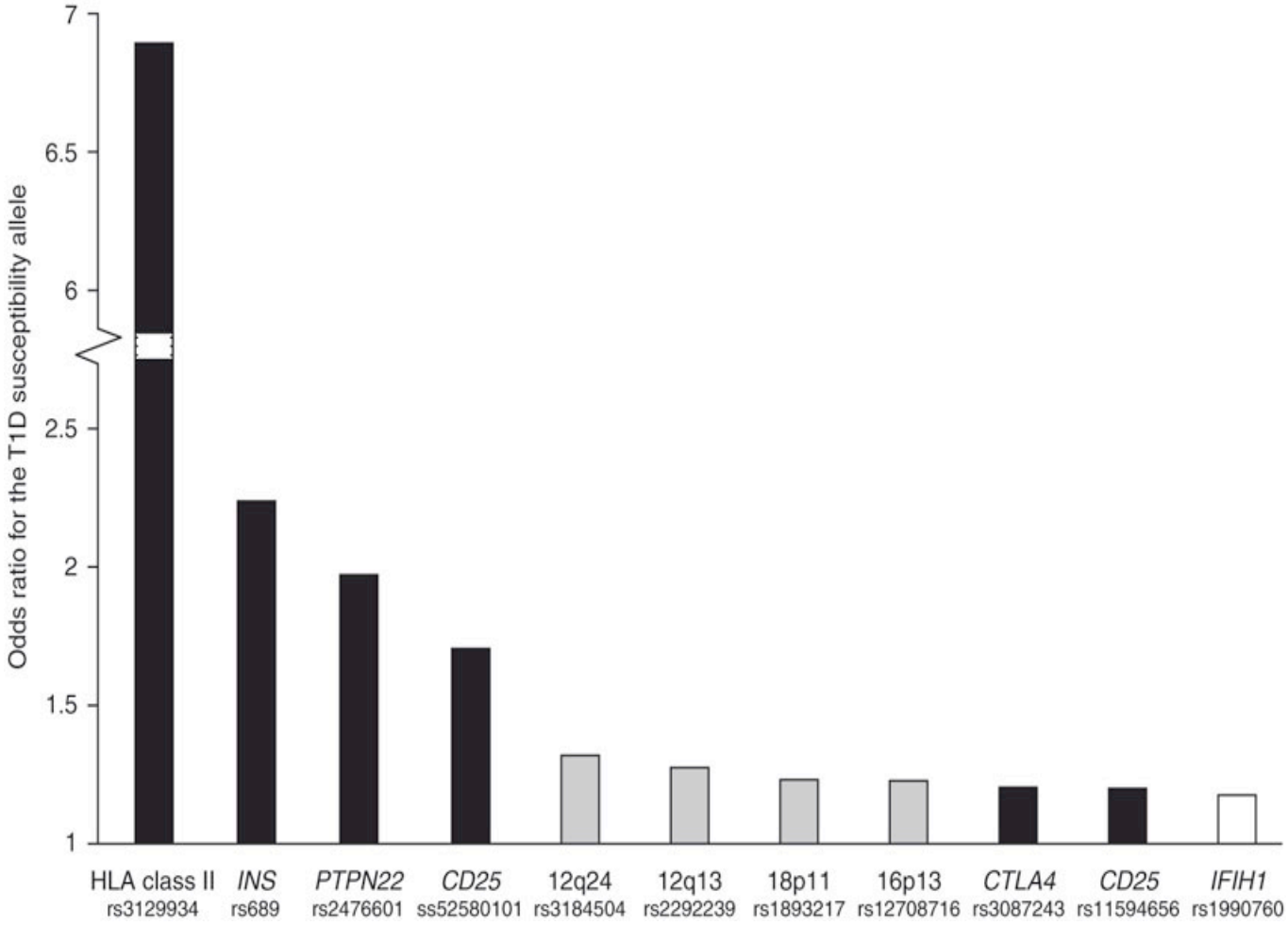
Genetic Susceptibility

Empiric risk of developing Type 1 diabetes

	Empiric Risk
First degree relatives of T1DM probands*	5-7%
Individuals without relatives with T1DM*	<1%
Children of affected father**	~6%
Children of affected mother**	~2%

These estimates are for North American Caucasian* and Scandinavian populations**

The Wellcome Trust Case Control Consortium (WTCCC) primary genome-wide association (GWA) scan in T1DM



Source: Todd JA et al. *Nature Genetics* 39, 857- 864, 2007

J. Noble

HLA

Human Leukocyte Antigen

human MHC

cell-surface proteins

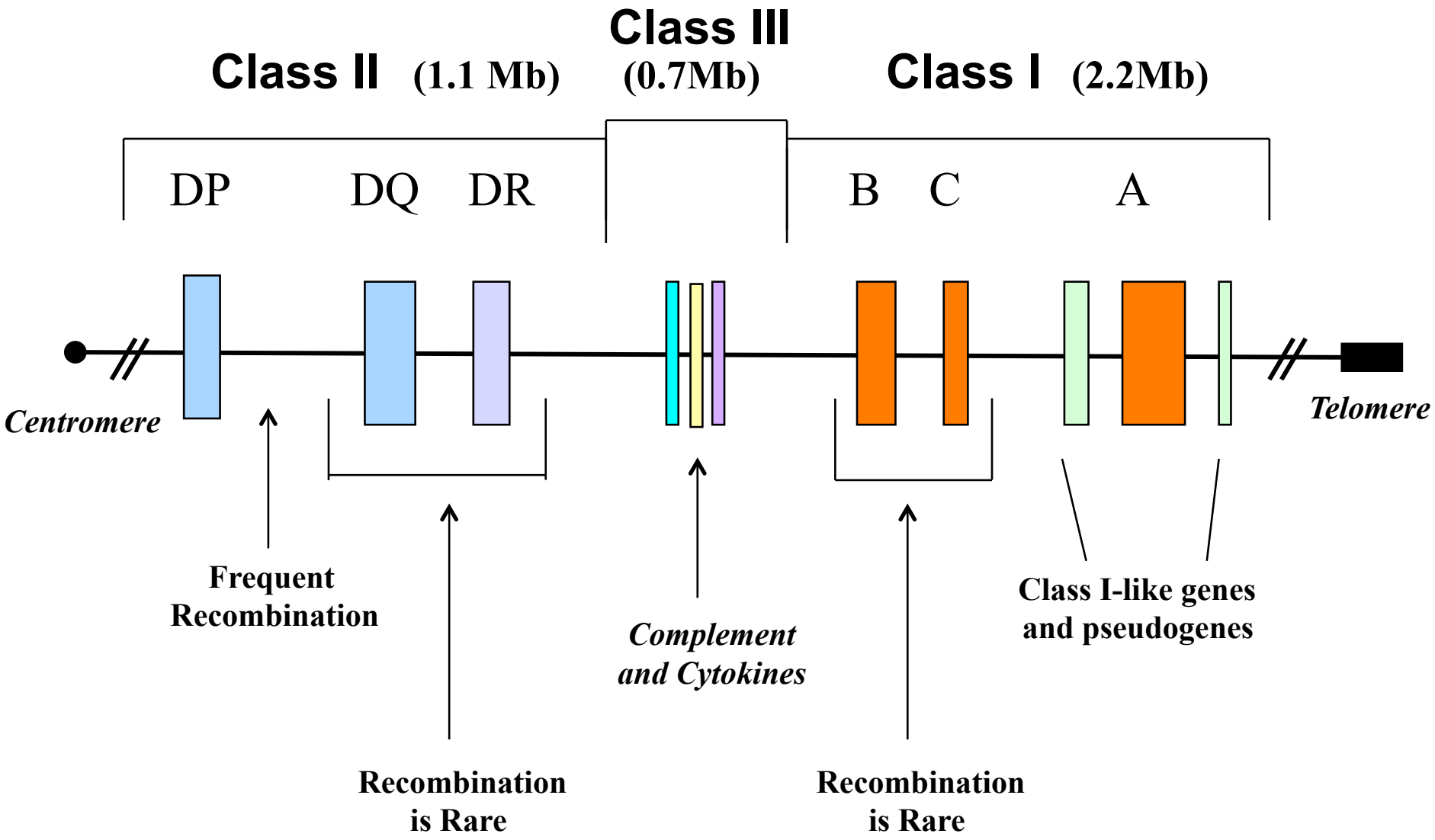
important in self vs. nonself distinction

present peptide antigens to T cells

CLASS I: A,B,C

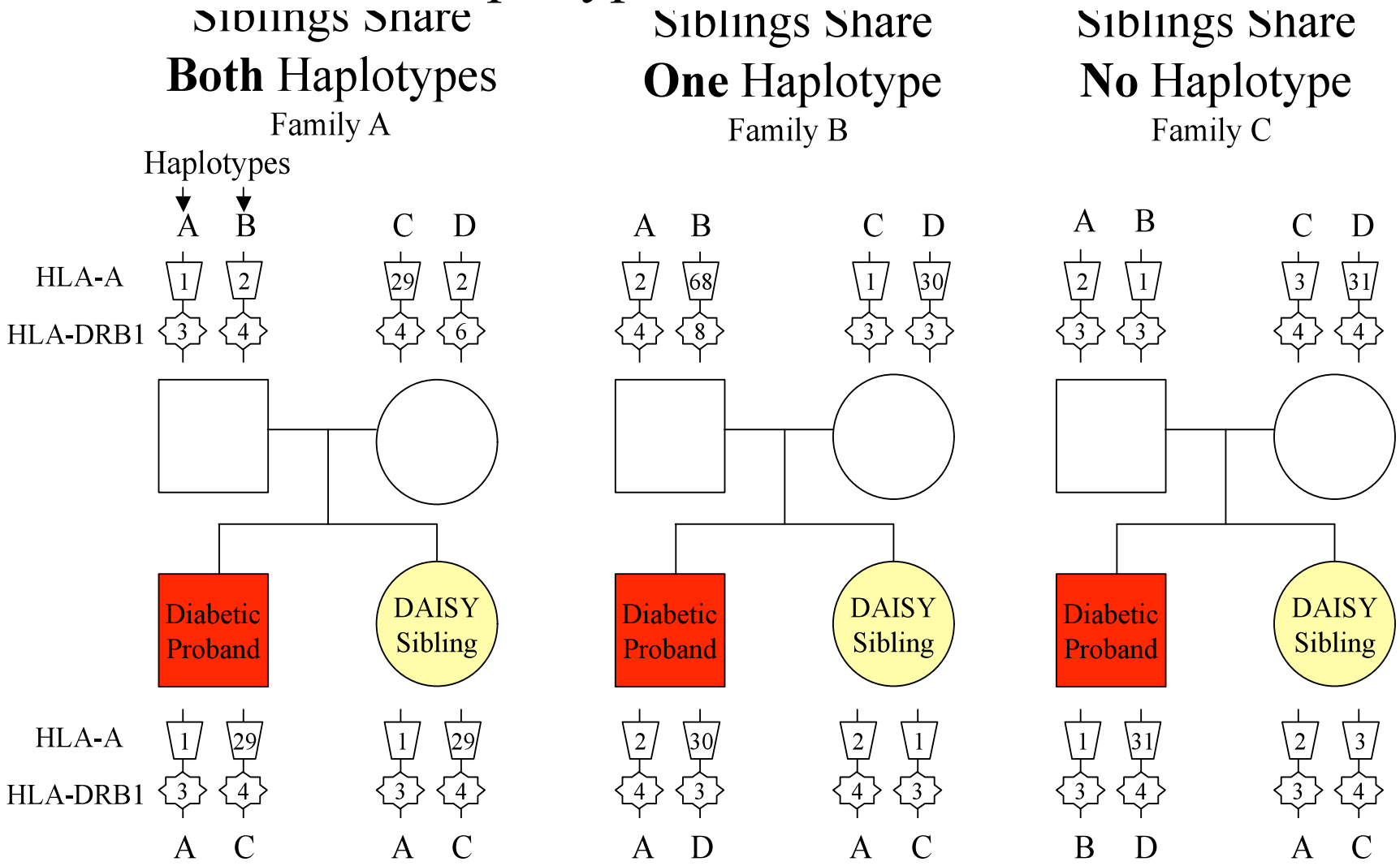
CLASS II: DR,DQ,DP

The Human Leukocyte Antigen Complex (6p21.31)

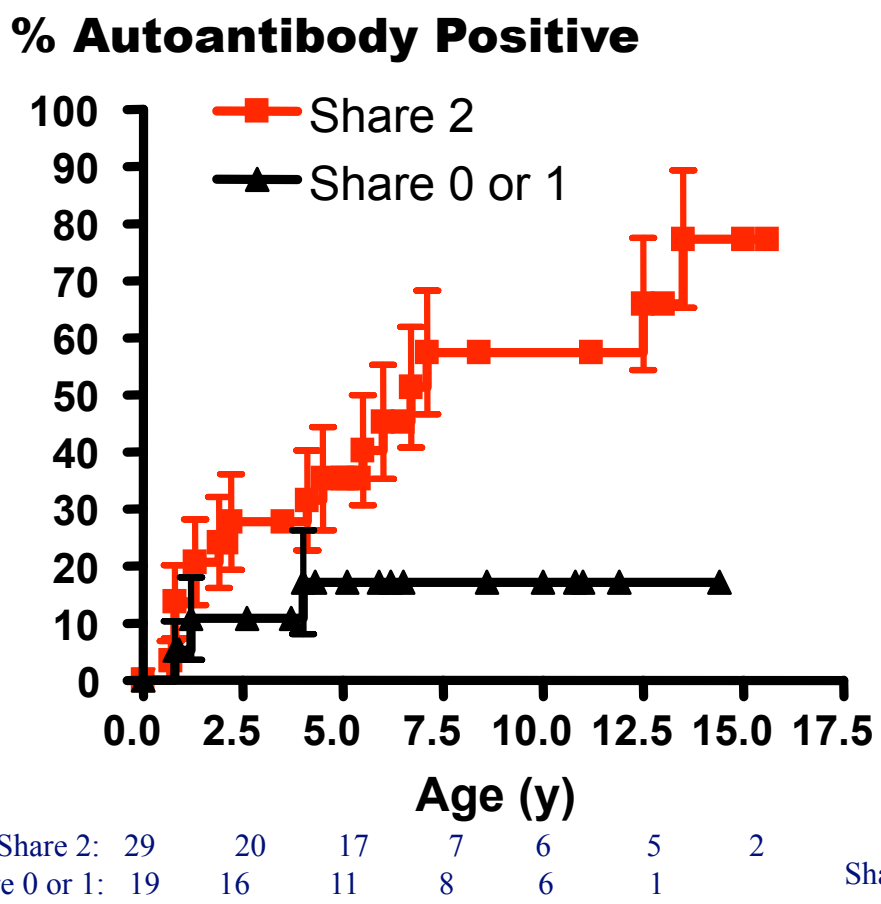


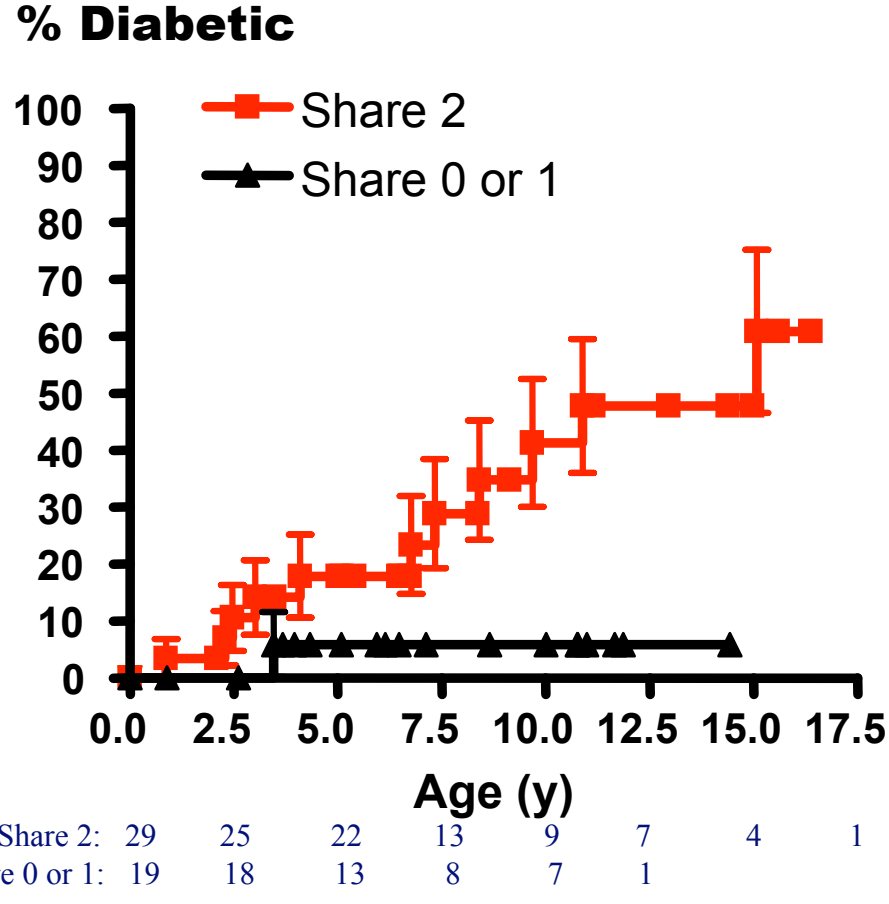
MHC Haplotype Sharing Increases DR3/4 Sibling Risk

Haplotype Determination:



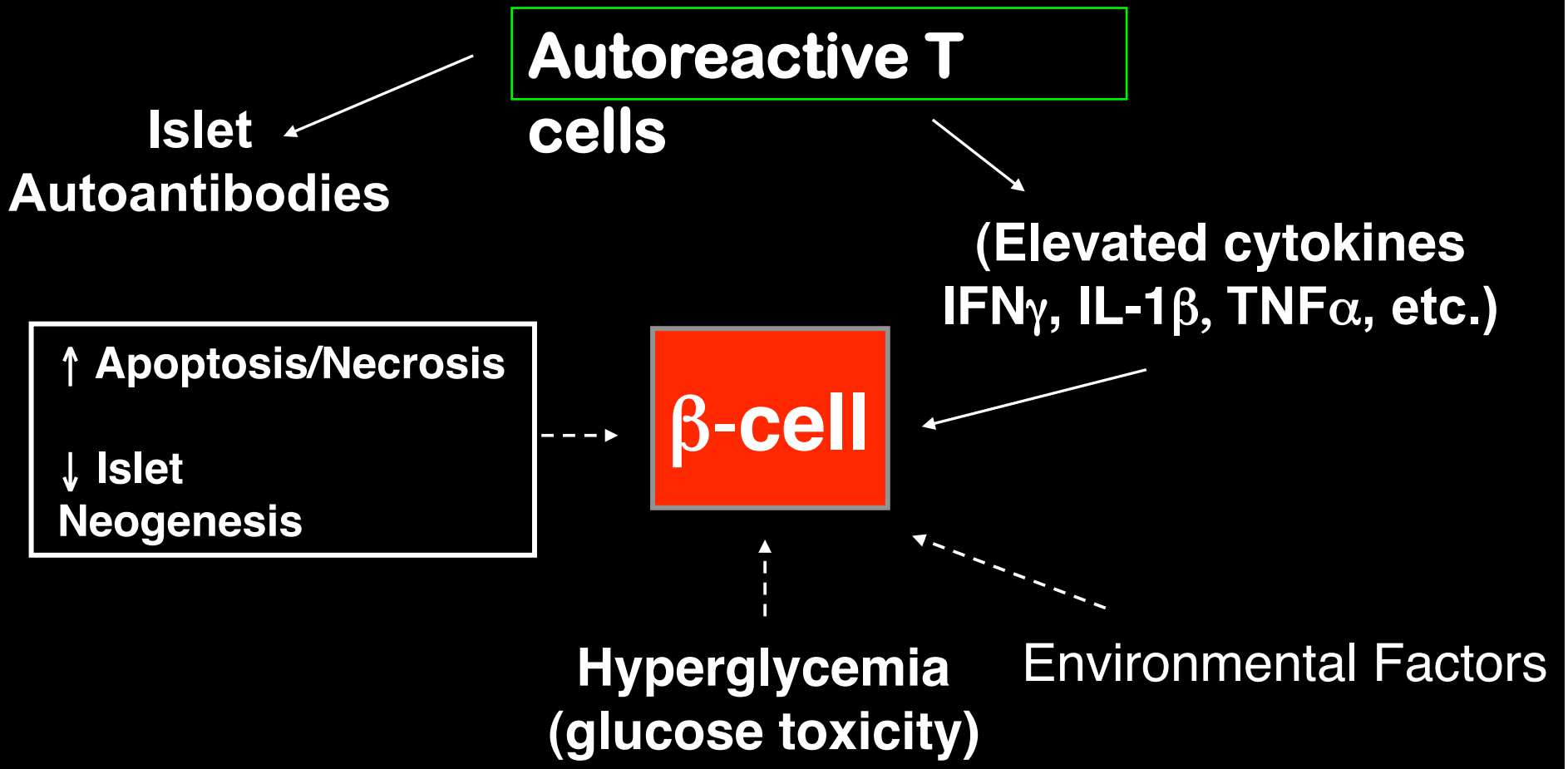
MHC haplotype sharing increases risk in DR3/4-DQ8 siblings





Source: Aly T et al. PNAS, 2006

Multiple Factors May Drive Progressive Decline of β-Cell Function



Environmental Factors

Congenital Rubella Syndrome

- 30% diabetic usually early T1DM, some T2DM
- incubation period 5-20 yrs
- HLA-DR3 or 3/4 in those with diabetes
- other autoimmune diseases (thyroid, AD)
- molecular mimicry with a 52kD autoantigen
- animal model - Syrian hamsters
- No diabetes after postnatal infection or MMR vaccination

Other Environmental factors involved in Type 1 diabetes pathogenesis

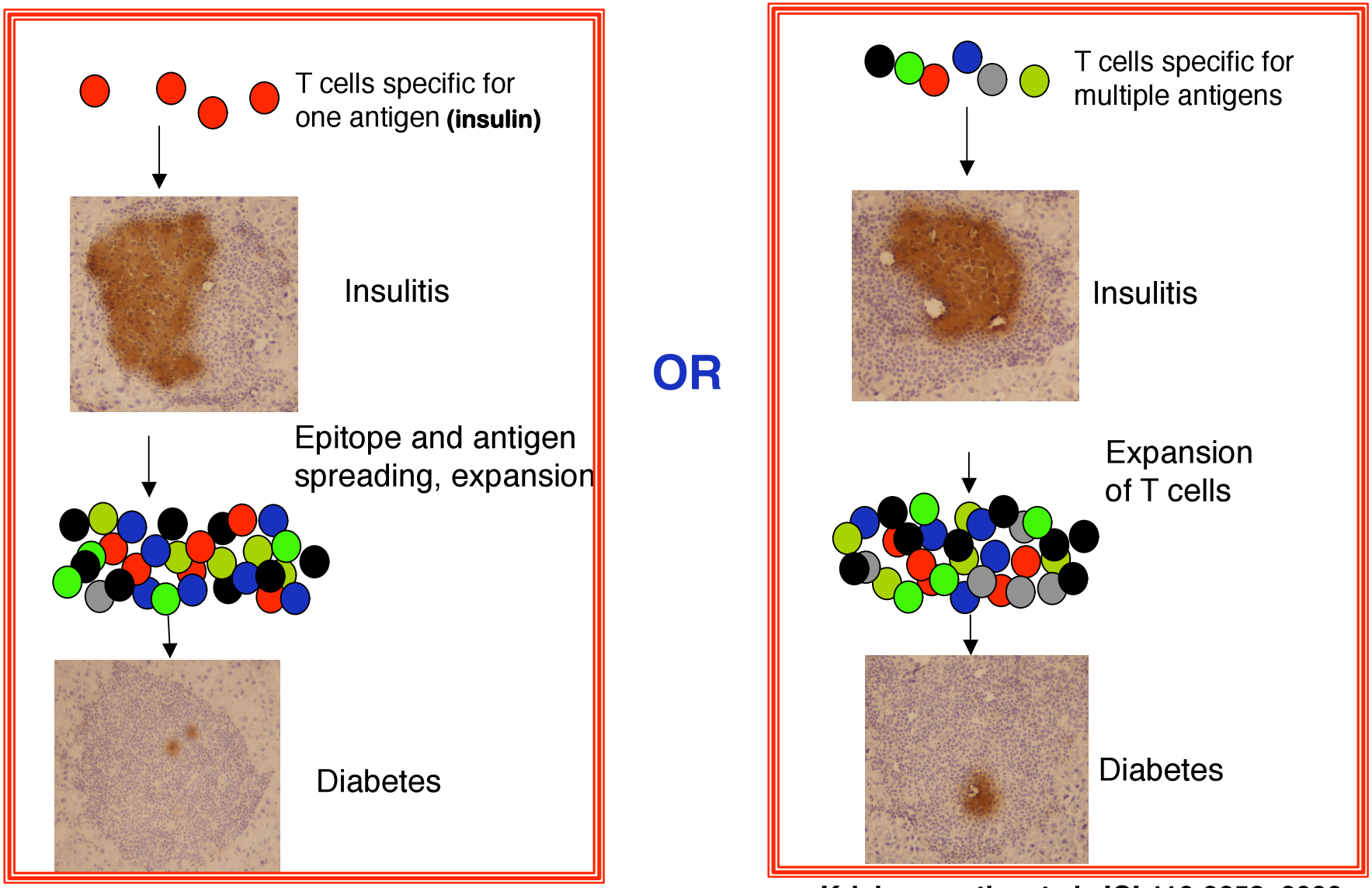
- Cocksakie B Virus ? Molecular mimicry with he islet autoantigen glutamic acid decarboxylase (GAD)
- Enterovirus ?
- Streptozotocine (low doses) ?

Loss of self tolerance to self-antigens

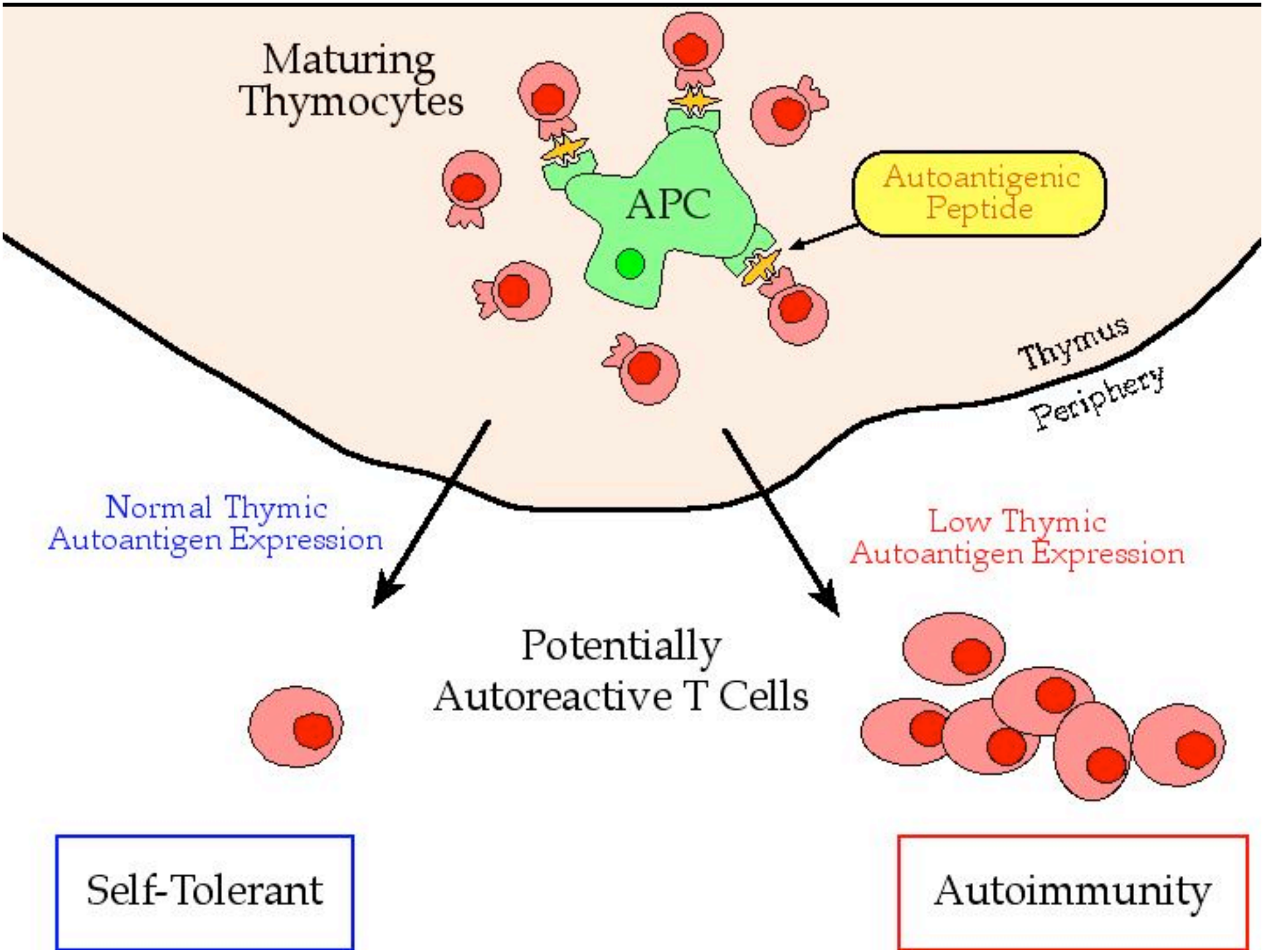
Autoantigens in Diabetes

- Insulin
- Glutamic acid decarboxylase (GAD65)
- Islet autoantigen 512aa (ICA512/IA-2)
- Zinc Transporter Znt8

Is there a primary antigen or immune response to multiple antigens required for autoimmunity?



Krishnamurthy et al JCI:116:3258, 2006


Maturing
Thymocytes
APC
Autoantigenic
Peptide
Thymus
Periphery
Normal Thymic
Autoantigen Expression
Low Thymic
Autoantigen Expression
Potentially
Autoreactive T Cells
Self-Tolerant
Autoimmunity

Role of T cells

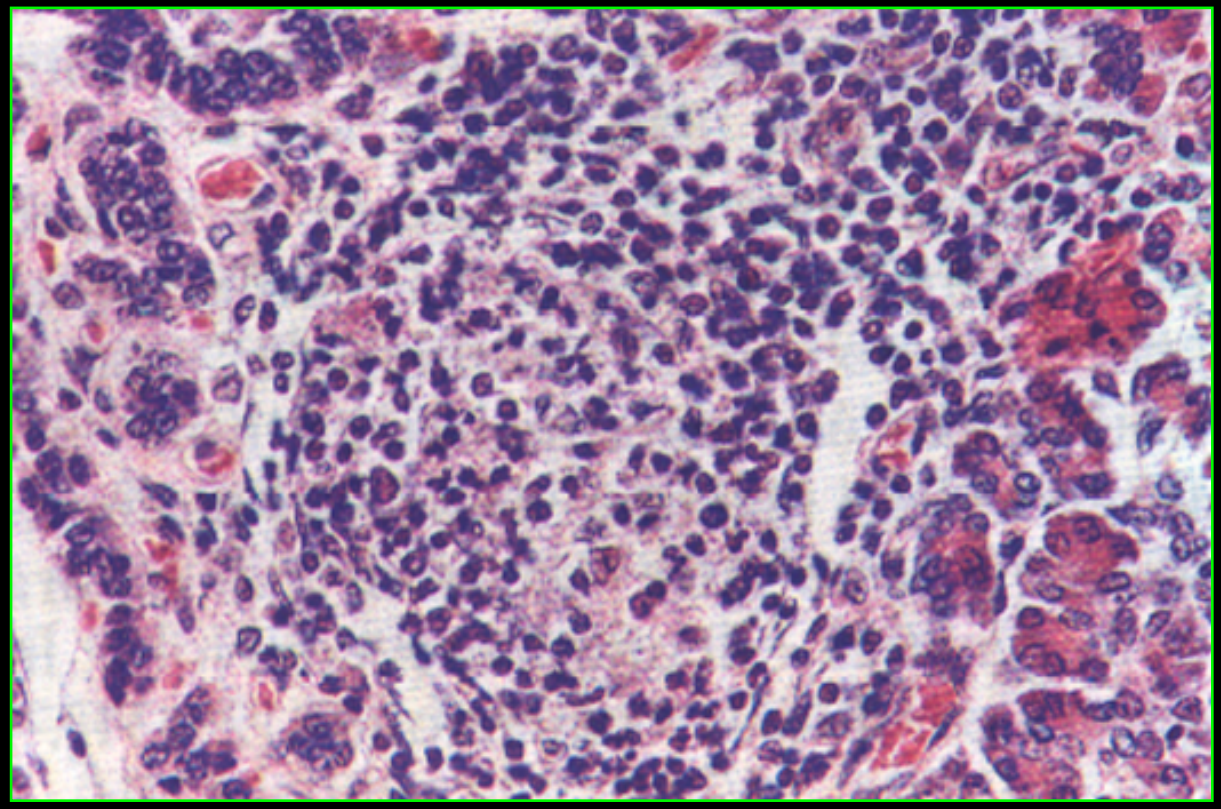
Pathogenic Cells in Type 1 diabetes

Cell-mediated Immunity

- CD4+ T cells-MHC class II molecules (APC) interaction
- CD8+ T cells-MHC class I molecules (APC) interaction
- NK cells ?
- Macrophages ?
- Dendritic cells ?

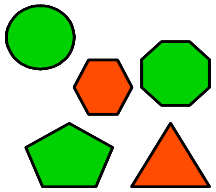
INSULITUS. PATIENT DIED FROM DKA

Conrad, B. et al. *Nature* 371:351 1994



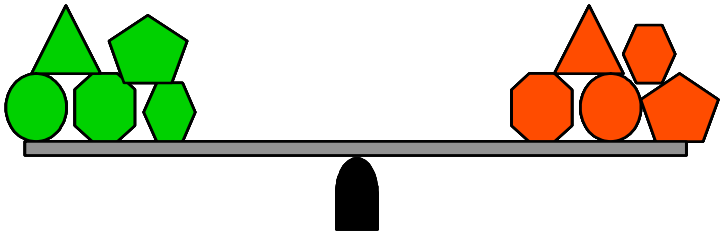
Type 1 diabetes pathogenesis: alteration between pathogenicity (T effector cells) and regulation (regulatory T cells)

T1D Development



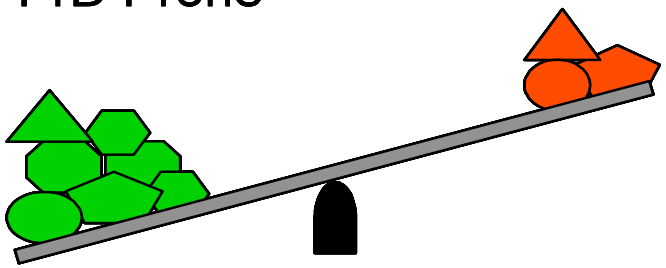
Contributing Factors

Normal



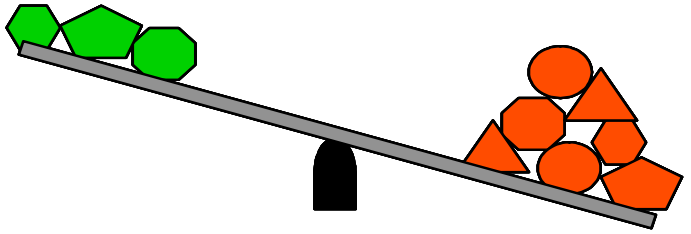
Pathogenicity Regulation

T1D Prone



Pathogenicity Regulation

T1D Protected



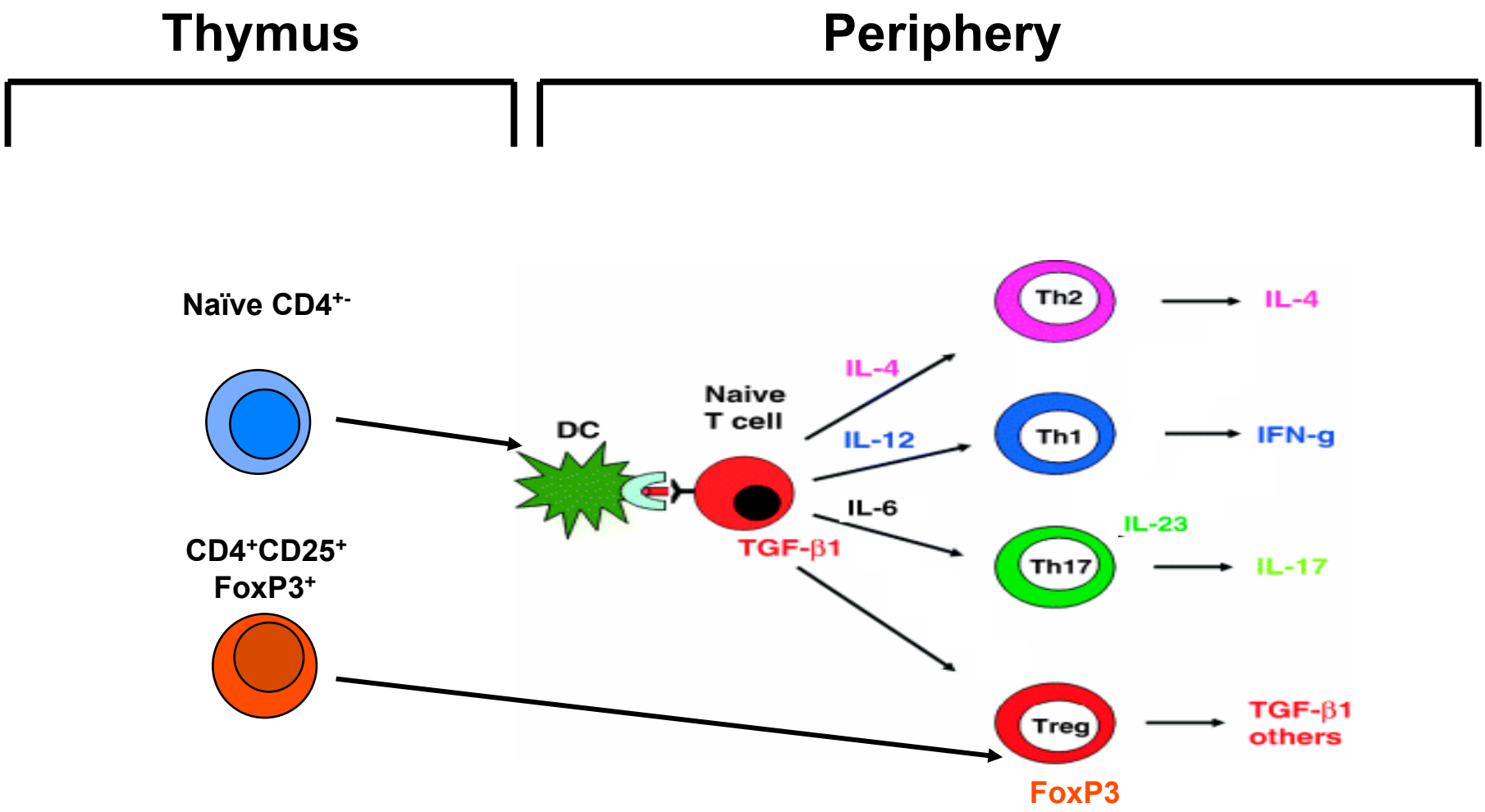
Pathogenicity Regulation

Example of regulatory T cell defect: X-linked autoimmunity-immunodeficiency syndrome (XLAAD)

Gene defect: *FOXP3*

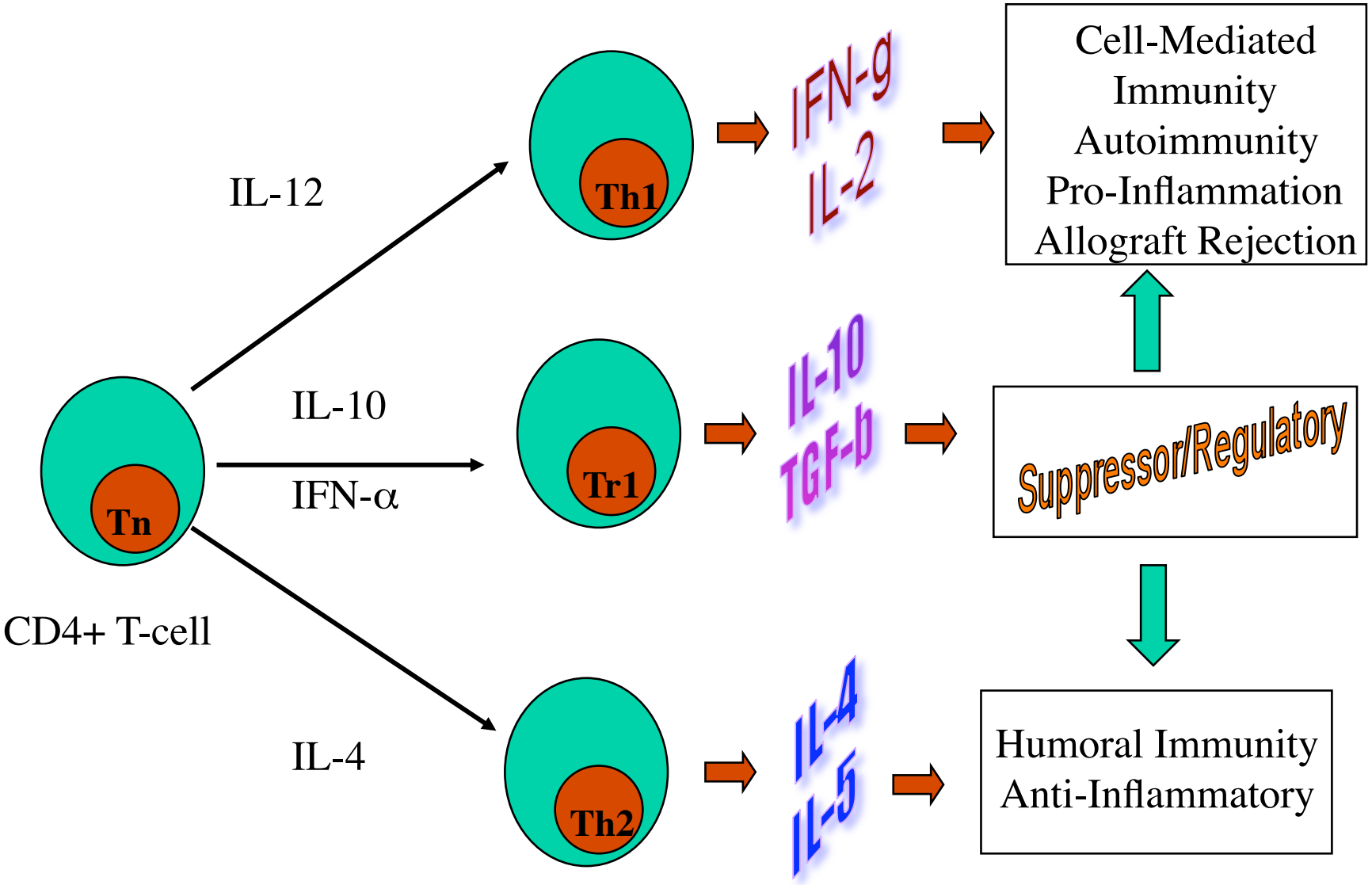
- ***This genetic defect can lead to Type 1 diabetes in the presence of other autoimmune disorders for abnormalities in regulatory T cell maturation.***

Regulatory T cells (Tregs)



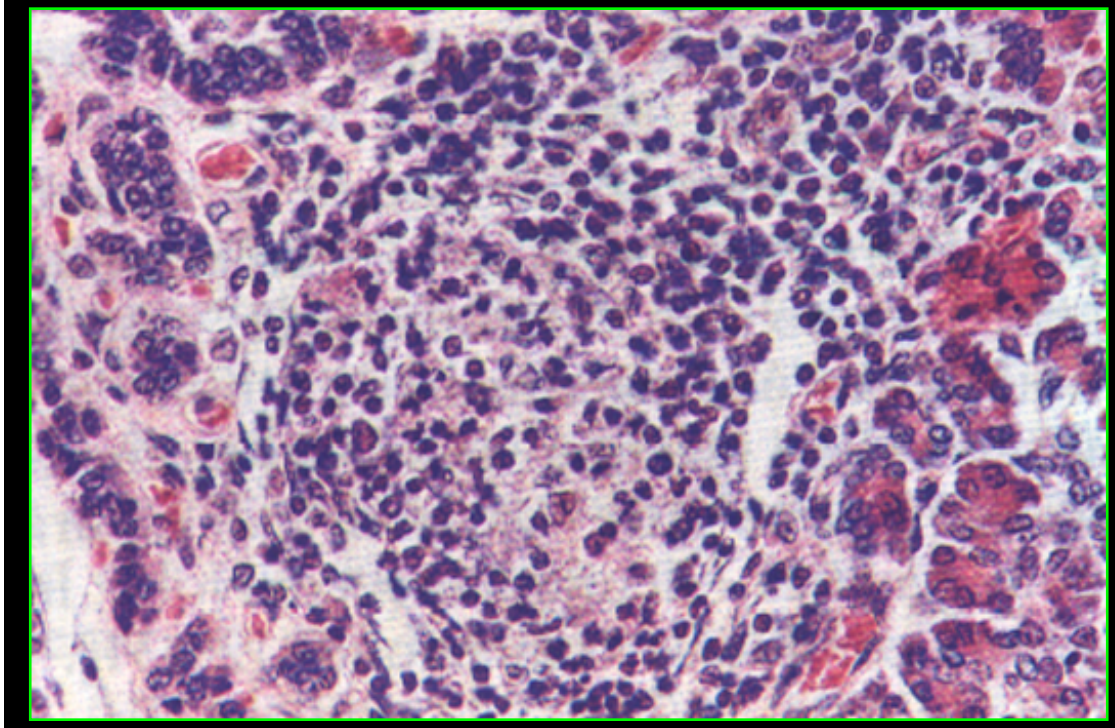
Role of cytokines

Differentiation of CD4+ T-cell Subsets



IL-β, IFN-γ, TNF-α

Oxidative Stress

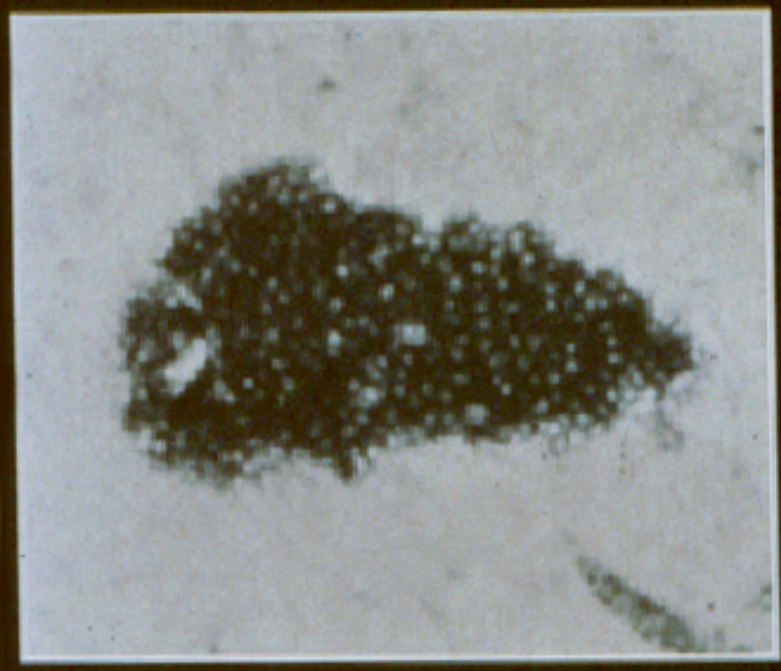


β-cell death

Nitric Oxide (NO) production

Role of autoantibodies

Cytoplasmic Islet-cell-antibody staining



Positive reaction

Negative reaction

Source: Diabetes Care, 1988

Islet Cell Autoantibody Assays

GAD65 Autoantibodies

Immunoprecipitation of *in vitro* transcribed/translated [^{35}S-Met] labeled antigen using patient serum. [CV: inter-assay: 13.2%; intra –assay: 12.2%]

IA-2 Autoantibodies

Immunoprecipitation of *in vitro* transcribed/translated [^{35}S-Met] labeled antigen using patient serum. [CV: inter-assay: 9.5%; intra–assay: 12.4%]

Insulin Autoantibodies (IAA)

New Radioimmunoassay [CV: inter-assay: 19.4%; intra-assay: 8%]

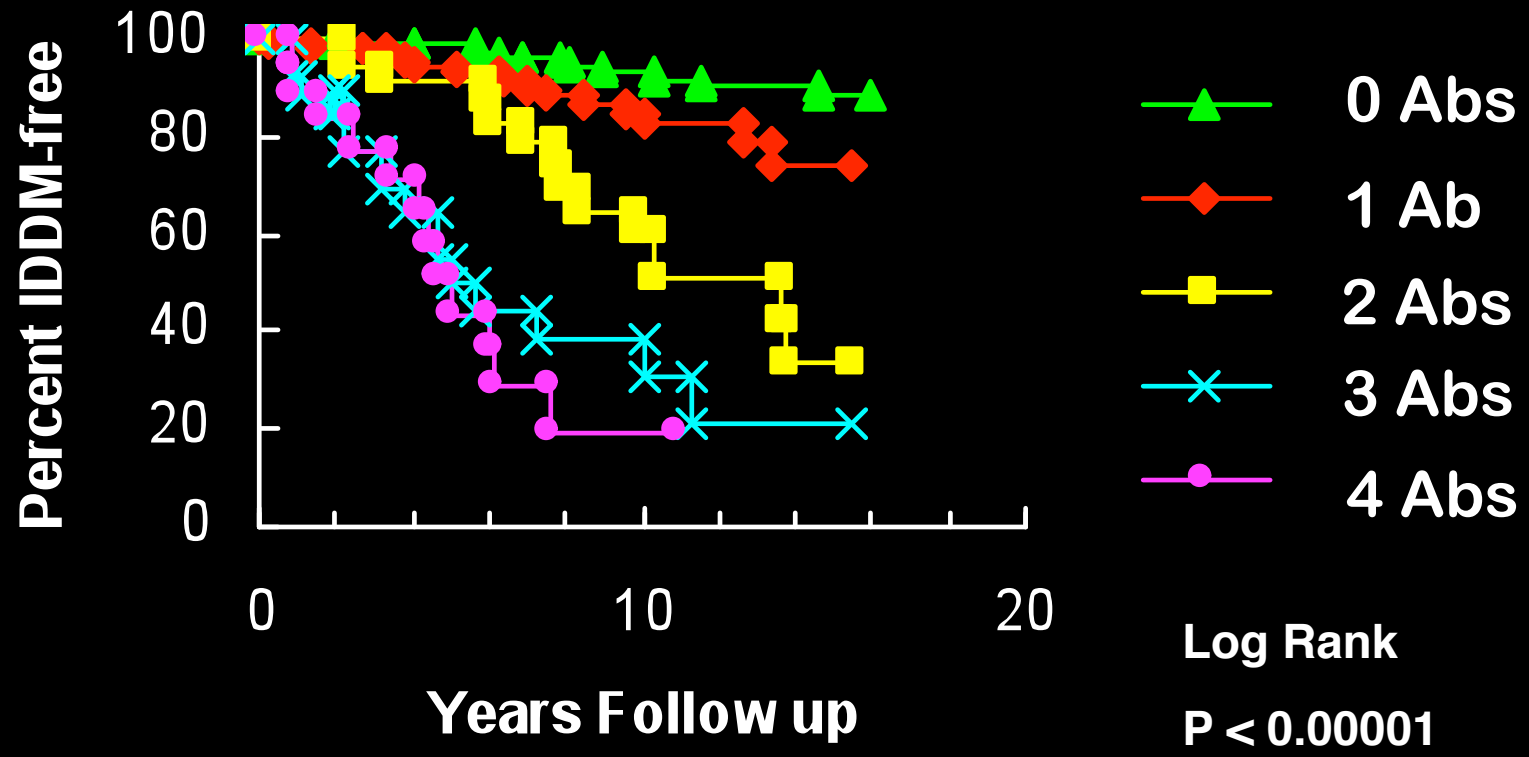
Islet Cell Antibodies (ICA)

Immunoperoxidase staining in rat and human pancreas

Prospective Studies in First Degree Relatives of T1DM Probands

Sibling/offspring cohort

Cumulative risk of developing clinical Type 1 diabetes in relatives of T1DM patients using islet autoantibodies (IAA, GAD65, IA-2, ICA)



Type I Diabetes TrialNet

http://www2.diabetestrialnet.org/

Objective: To determine whether any immunomodulatory therapy can ameliorate insulin secretion in newly diagnosed T1DM (17-40 yr of age) and to ultimately prevent T1DM onset in first-degree relatives of T1DM probands. First trials in relatives started in 2003.

Criteria for enrolling T1DM patients in TrialNet: ≥ 2Ab to islet antigens.

Conclusions

- Type 1 diabetes mellitus is a polygenic disease. Although at least 19 T1DM -related candidate genes have been identified, polymorphic regions within the HLA complex confers the strongest diabetogenic effect.
- CD4+ and CD8+ T cell responses to islet autoanti gens (insulin, GAD65 and IA-2) are pathogenic.
- A defect of Regulatory T cells in suppressing pathogenic autoimmune responses is associated with Type 1 diabetes.
- The proinflammatory cytokines IL-1β, IFN-γ and TNF-α can cause β cell death (increased NO production).
- Gene defects in FOXP3 and AIRE cause multiple autoimmune disease (APECED, APS-I respectively) including Type 1 diabetes
- The presence of multiple autoantibodies to insulin, GAD65, IA -2 are high risk markers of Type 1 diabetes progression.