Tolerance, Autoimmunity, Allogenicity (2nd part)

Autoimmunity

Allogenicity

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Tolerance, Autoimmunity, Allogenicity (2nd part)

III- Autoimmunity

A – AID classification and examples

B – animal models

C – Why do AID occur?

D – Diagnosis, Treatments?

IV- Allogeneicity and transplantation tolerance

A – Concept and mechanism of Allogenicity and MLR

B – Classification & Mechanism of Graft rejection

C – GVHD

D – Biotherapies?

III - Autoimmunity

Autoimmunity

- **Definition: immune response against self (auto-) antigen**

- **General principles:**
  - **Significant health burden, 7 % of population (still increasing)**
  - **Multiple factors contribute to autoimmunity, including genetic predisposition, infections, environment**
  - **Fundamental problem is the failure of self-tolerance**

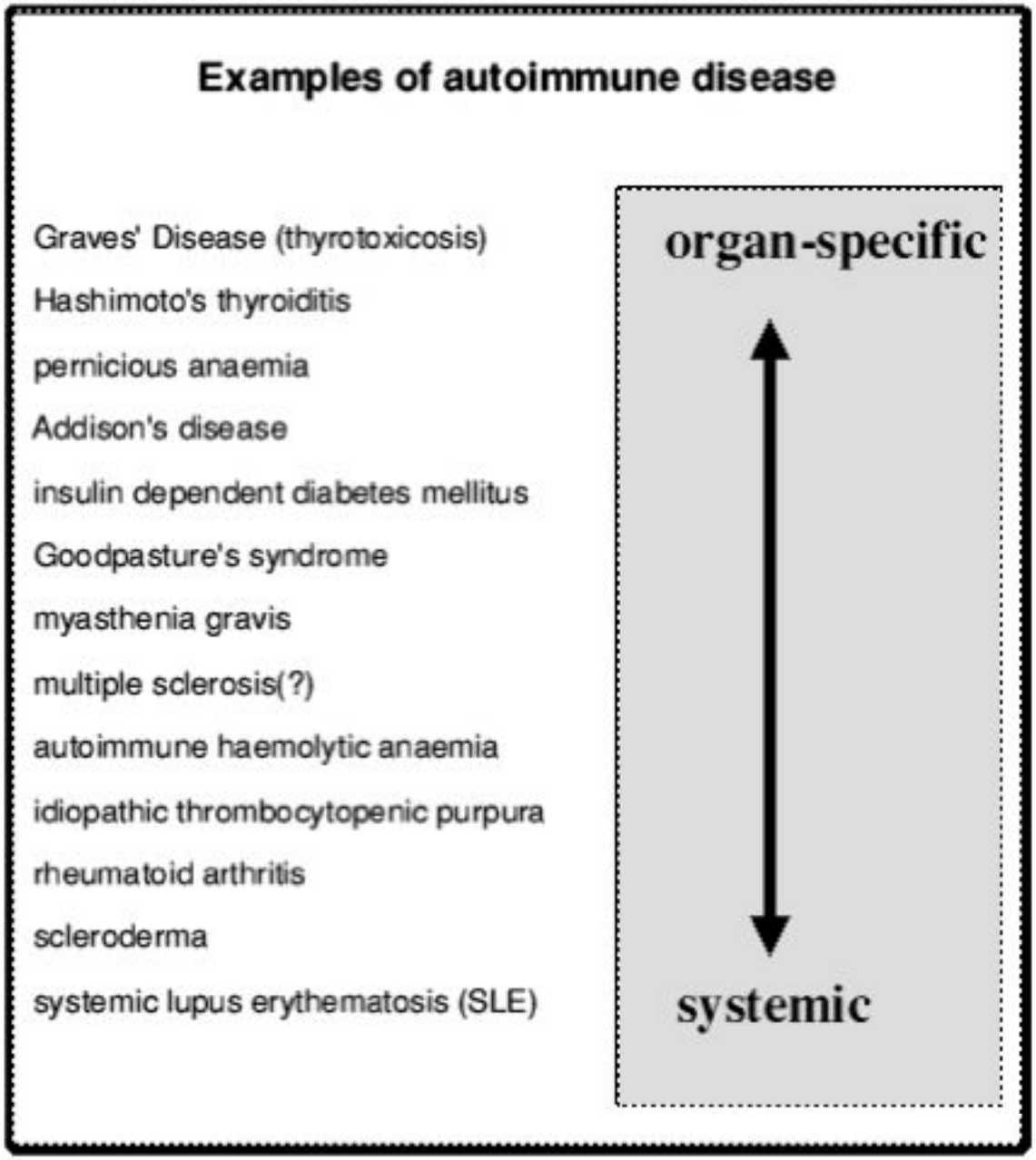
- **Problems:**
  - **Failure to identify target antigens, heterogeneous disease manifestations, disease usually presents long after initiation**

  - The causes of the disease outbreak are still unknown

- **Characteristics: evolutive, progression by surges**

III- Autoimmunity

A - AID classification and examples



Hypersensibility

Coombs and Gell classification

Comparison of hypersensitivity types

Type	Alternative names	Often mentioned disorders	Mediators
I	Allergy (immediate)	• Atopy • Anaphylaxis • Asthma	• IgE and IgG4
II	Cytotoxic, antibody-dependent	• Autoimmune hemolytic anemia (RBCs) • Thrombocytopenia (Platelets) • Erythroblastosis fetalis (Mother Abs cross Placenta) • Goodpasture's syndrome (lungs & Kidneys) • Graves' disease *see type V explanation below • Myasthenia Gravis *see type V explanation below	• IgM or IgG • (Complement)
III	Immune complex disease	• Rheumatoid arthritis • Serum sickness • Arthus reaction • Systemic lupus erythematosus (SLE) • Extrinsic allergic alveolitis (Hypersensitivity pneumonitis)	• IgG • (Complement)
IV	Delayed-type hypersensitivity[2] [3](DTH), cell-mediated immune memory response, antibody-independent	• Contact dermatitis • Mantoux test • Chronic transplant rejection • Multiple sclerosis [4] • T1D • Oophoritis • Prostatis ...	• T-cells
V	Autoimmune disease, receptor mediated (see below)	• Graves' disease • Myasthenia Gravis	• IgM or IgG • (Complement)

Complement lysis

Ag-Ab accumulation

T cell-mediated Autoimmunity

Agonists or bloquing Ab

Wikipedia 2011

Type II: Antibody-mediated diseases

Autoimmune disease	Autoantigen	Consequence
Antibody against cell-surface or matrix antigens (type II)		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes anemia
Autoimmune thrombocytopenia purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness

Figure 11-1 part 1 of 3 The Immune System, 2/e (© Garland Science 2005)

Type II-V : Graves' disease

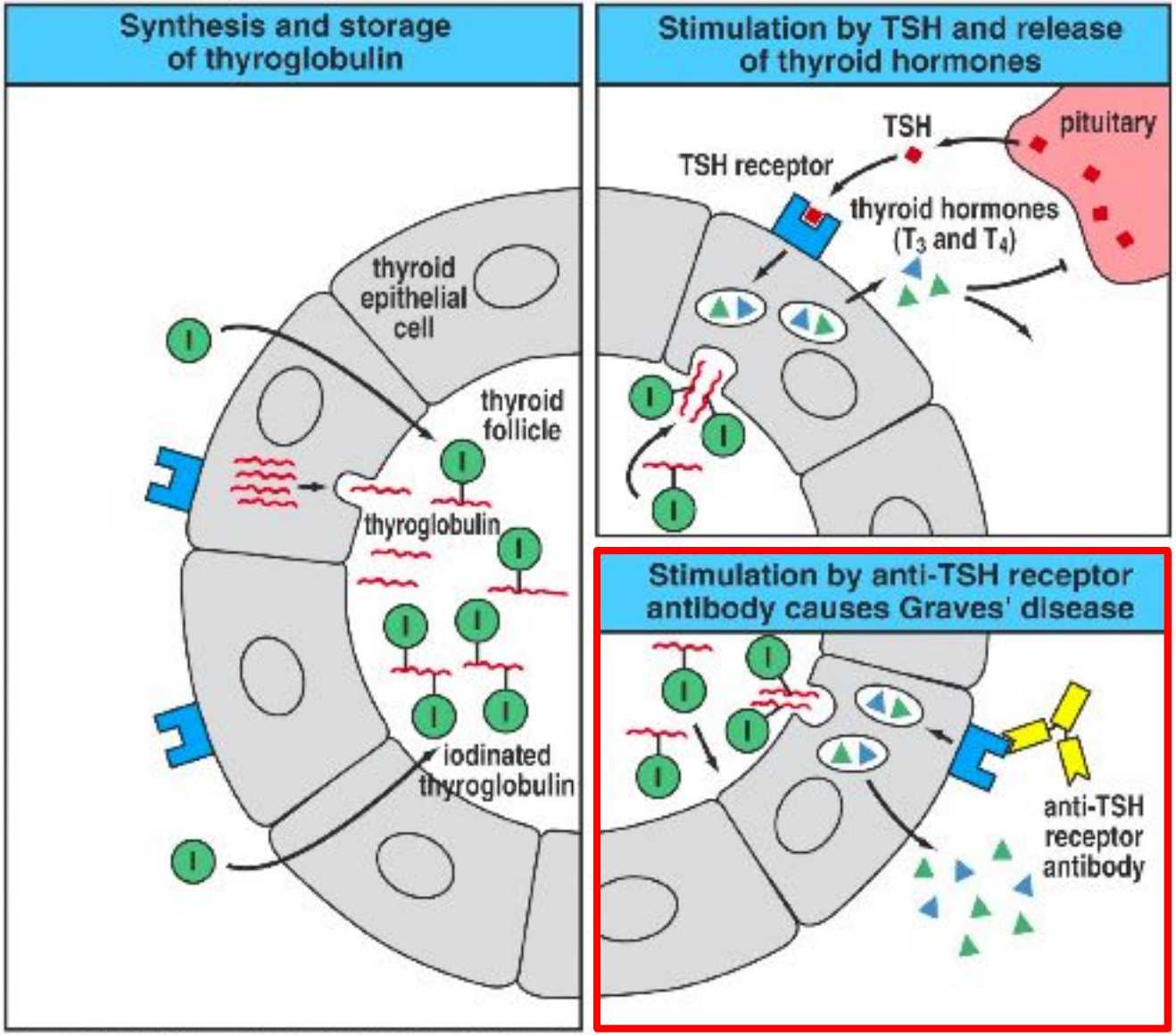


Figure 11-5 The Immune System, 2/e (© Garland Science 2005)

Thyroid stimulating immunoglobulins recognize and **bind** to the TSH receptor (thyrotropin receptor). It **mimics** the TSH to that receptor and **activates the secretion** of

- thyroxine (T4)
- triiodothyronine (T3)

and the actual TSH level will **decrease** in the blood plasma.

This leads to an **enlargment** of the thyroid and very high levels of circulating thyroid hormones

The hormonal dysregulation induces heartbeat, muscle weakness, disturbed sleep, and irritability.

affects up to 2% of the female population, sometimes appears after childbirth, Hereditary factors are the major risk factor for the development of Graves disease, with "79% of the liability to the development of GD ... attributable to genetic factors". Smoking and exposure to second-hand smoke is associated with the eye manifestations but not the thyroid manifestations.

Graves' disease: Proof that it's antibody mediated

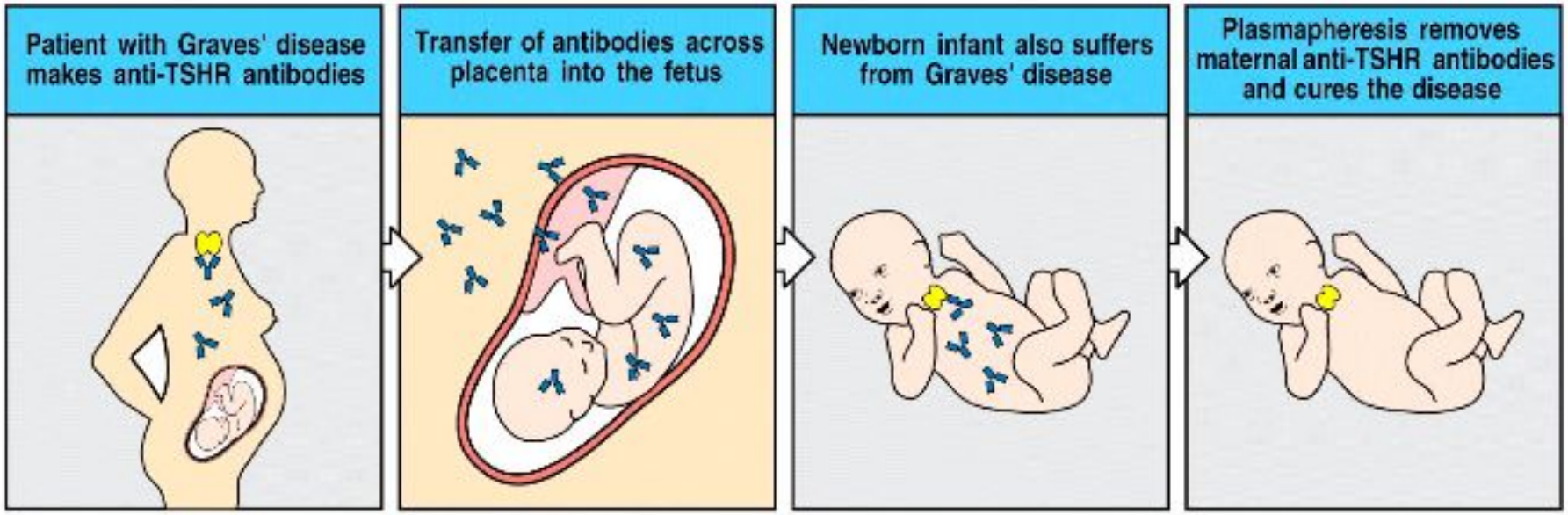


Figure 11-7 The Immune System, 2/e (© Garland Science 2005)

Myasthenia Gravis

(Type II-V)

In this disease, autoantibodies to the Acetylcholine receptor block neuromuscular transmission from cholinergic neurons by blocking the binding of acetylcholine and by causing downregulation (degradation) of its' receptor.

Type III: Immune-complex mediated diseases

Autoimmune disease	Autoantigen	Consequence
Immune-complex disease (type III)		
Subacute bacterial endocarditis	Bacterial antigen	Glomerulonephritis
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, arthritis

Figure 11-1 part 2 of 3 The Immune System, 2/e (© Garland Science 2005)

Review: Immune complex formation

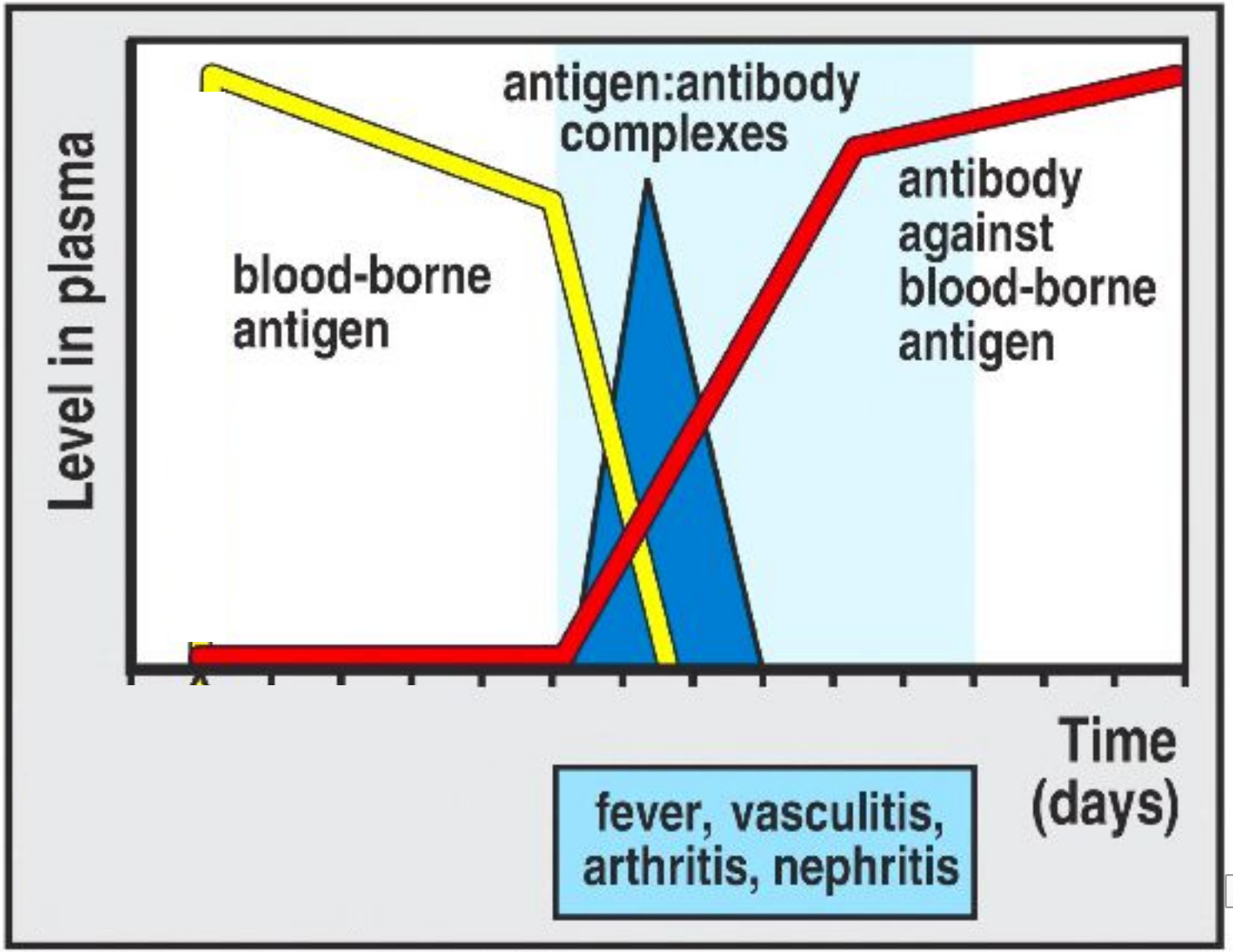


Figure 10-32 The Immune System, 2/e (© Garland Science 2005)

Figure 11-10 The Immune System, 2/e (© Garland Science 2005)

(SLE)

Systemic Lupus Erythematosus (SLE)

- Systemic diseases such as SLE and vasculitis almost certainly result from autoantibody-antigen complexes and their consequences. Circulating antibodies to constituents of the cell surface, cytoplasm, and nucleus
  - Anti-DNA, anti-histone, anti-sRNP
- Certain organs are especially sensitive to immune complex deposition particularly the kidney. SLE patients possess a wide variety of autoantibodies to both cytoplasmic and nuclear antigens.
- The presence of IgG anti double- stranded DNA is characteristic of this condition (Note: IgM anti-ds DNA is NOT pathogenic).
- Symptoms include rash, arthritis, glomerulonephritis, vasculitis.

Type IV: T cell-mediated diseases

Autoimmune disease	Autoantigen	Consequence
T cell-mediated disease (type IV)		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Multiple sclerosis	Myelin basic protein, proteolipid protein	Brain degeneration. Paralysis
Celiac disease	Gluten modified by tissue transglutaminase	Malabsorption of nutrients Atrophy of intestinal villi

Figure 11-1 part 3 of 3 The Immune System, 2/e (© Garland Science 2005)

T cell mediated effects (cellular immune)

- Direct T cell cytotoxicity via CD8+ CTL
- Self-destruction of tissue cells induced by cytokines, eg, TNFa
- Recruitment and activation of macrophages leading to bystander tissue destruction
- Induction of target tissue apoptosis by the T cell membrane protein **FasL**

- Production of autoantibodies

Type I Diabetes: a T cell-directed attack against the β-cells of the pancreatic islet

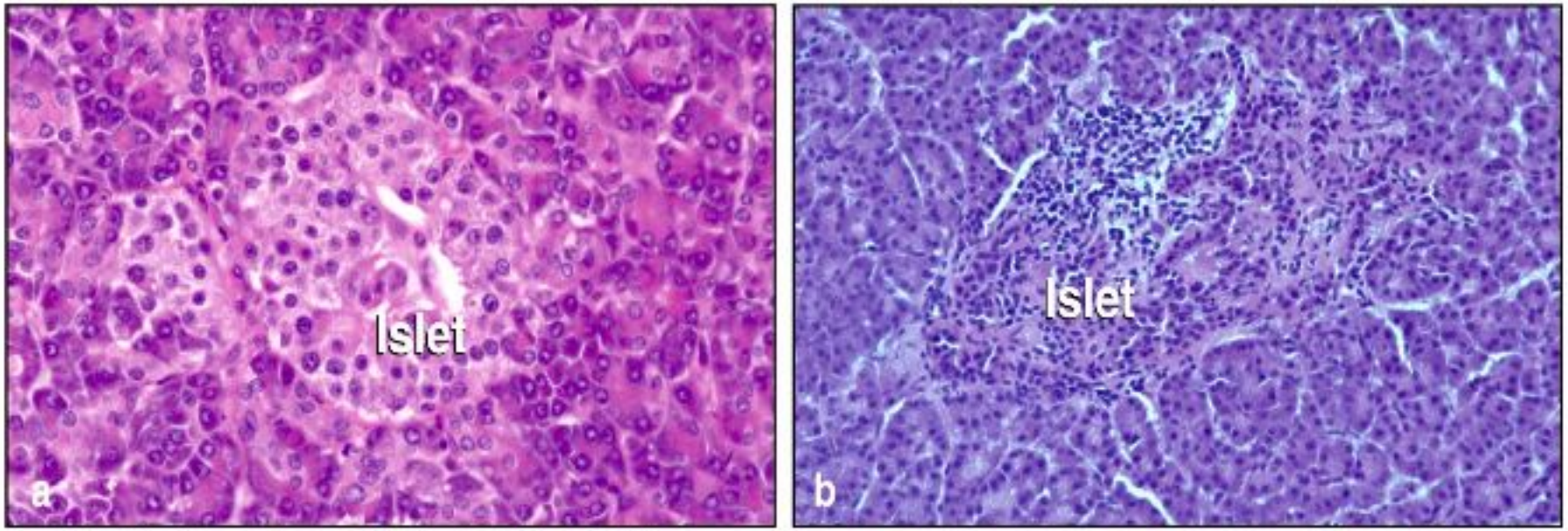


Figure 11-8 The Immune System, 2/e (© Garland Science 2005)

Type I Diabetes

- T cell response to antigens expressed in the β-cells of the islets
  - Proinsulin/Insulin, GAD, I-A2
  - T cell response is Th1 "like", makes g-IFN and helps recruit a tissue/cell destruction response
- >90% islet destruction needed for the disease to be expressed
- Patients also have autoantibodies to islet antigens

Monogenic autoimmune diseases