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							
Туре	Alternative names	Often mentioned disorders	Mediators				
1	Allergy (immediate)	AtopyAnaphylaxisAsthma	• IgE and IgG4				
II	Cytotoxic, antibody-dependent Complement lysis	 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) 				
Ш	Immune complex disease Ag-Ab accumulation	 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) Agonists or bloquing Al	 Graves' disease Myasthenia Gravis 	• / / or lga				

Wikipedia 2011

Type II: Antibody-mediated diseases

Autoimmune disease	Autoantigen Consequenc				
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 gpllb:Illa	Abnormal bleeding			
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Giomerulonephritis, 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)





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

affects up to 2% of the female population, sometimes appears after childbirth, Hereditary factors are the major risk factor for 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.

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.

Graves' disease: Proof that it's antibody mediated



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



Myasthenia Gravis

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



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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			

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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 celldirected attack against the βcells 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 βcells 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

