جامعة الملك سعود
King Saud University

This block's study mood

Endocrine Disorders

Color code:
Important in red
Extra in blue

Immunology
MED438

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KING SAUD UNIVERSITY

Reviewed by Razan AlRabah & Ibrahim ALDakhil

Editing file

Objectives

- To recognize that many endocrine disorders are organ-specific autoimmune diseases.
- To understand the mechanisms of damage which take place at endocrine glands and their consequences.
- To know the important examples of autoimmunity which affect different endocrine glands and the pathogenesis of these disorders.
- To actually read the objectives for once

Review (Extra)

Mechanisms of Autoimmunity

Sequestration	Some self antigens are hidden in tissues and are normally not sensed by the immune system. When those self antigens are exposed to T cells (as a result of infection/trauma), an autoimmune reaction occurs. e.g. Sympathetic Ophthalmia: Trauma in one eye releases the sequestered intraocular antigens to the Lymph node (activates T cells) The T cells will then move to the undamaged eye and attack the self-antigens there.
Molecular Mimicry	Viruses and bacteria possess similar/identical antigenic determinants to those of normal cells. e.g. HIV p24 antigen identical to the IgG constant region
Abnormal MHC II Expression	Abnormal expression of MHC Class II on non-APC cells (e.x. pancreatic β cells) due to IFNγ production (induced by a viral infection) causes self-reactive T cells to destroy them e.g. Type I Diabetes
Polyclonal B Cell Activation	Happens when a polyclonal B cell (nonspecific) is activated by certain viruses and bacteria without the help of T cells (T-independent).This self-reactive plasma cell will proliferate and eventually produce polyclonal antibodies (mainly IgM), some of which will be autoantibodies e.g. EBV causing infectious mononucleosis

Autoimmune diseases can be broadly divided into:
1- Systemic: e.g. SLE and Rheumatoid Arthritis
2- Organ-specific (discussed in this lecture)

Endocrine Disorders

Many endocrine disorders are organ-specific autoimmune diseases

Response is directed to a target antigen unique to a single organ, with manifestations largely limited to that organ

The damage may be directly mediated by:

- Humoral immunity (Autoantibodies overstimulate or block the normal function of the target organ)
- Cell-mediated immunity
- Both (e.g. **Hashimoto** and possibly Addison's)

Examples

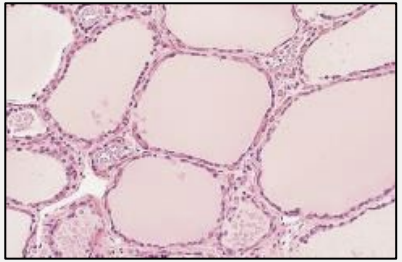
Thyroid	Hashimoto's disease (Hypothyroidism): Autoantibodies against Thyroid Peroxidase Primary Myxoedema (Hypothyroidism): Atrophy of the thyroid gland Graves' disease (Hyperthyroidism): Autoantibodies against TSH receptor
Pancreas	Type I Diabetes: Abnormal MHC Class II expression on β cells
Adrenal	Addison's disease: Insufficient steroid hormones (chronic adrenal gland disorder)
Gonads	Autoimmune Oophoritis: Ovarian inflammation Autoimmune Orchitis: Testicular pain involving swelling, inflammation, and infection
Pituitary	Lymphocytic hypophysitis: Low production of one or more pituitary hormones due to autoimmunity/autoantibodies

Thyroid Diseases

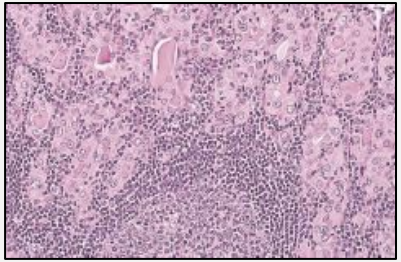
Chronic Lymphocytic Thyroiditis (Hashimoto)

Prevalence	Frequently seen in middle-aged women (M:F is 1:3) Associated with HLA II DR4 (predisposing) and HLA II DR13 (protective role)
Pathophysiology	Anti-thyroid peroxidase and Anti-thyroglobulin antibodies (both protein antigens are involved in Iodine uptake) with sensitized TH1(inflammatory) cells specific for thyroid antigens (Delayed-Type Hypersensitivity) Auto-abs bind to the proteins → Interfere with iodine uptake → Decreased production of thyroid hormones The DTH response is characterized by: - Intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells (forming follicles and germinal centers) The inflammatory response will result in a goiter (physiological response to hypothyroidism) (Recall the Trophic effect of TSH, which will be elevated in Hashimoto)
Clinical features	Hypothyroidism: - Fatigue & Loss of energy - Weight gain - Mental slowing - Cold intolerance - Goiter

Normal thyroid gland



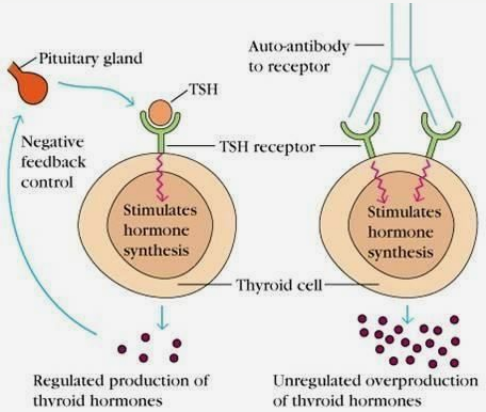
Hashimoto's intense lymphocytic infiltration



Thyroid Diseases

Graves' disease

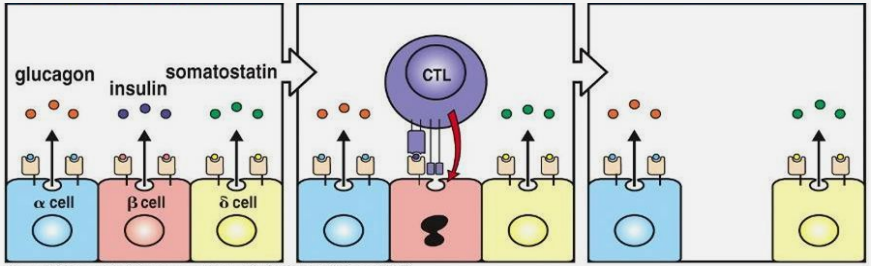
Prevalence	Less common than Hashimoto's disease (M:F up to 1:7) Associated with HLA II DR3 (predisposing), HLA II DR7 (protective role), and HLA B8
Physiology	T3/T4 production is normally monitored by TSH. It binds to a receptor on Thyroid cells and activates the Adenylate Cyclase pathway to stimulate the synthesis of those hormones. (TSH is controlled by -ve feedback)
Pathophysiology	In Graves' disease, auto-antibodies bind the TSH receptor and mimic its normal actions (activating AC pathway). Unlike TSH, the long-acting thyroid stimulating (LATS) antibodies are unregulated and overstimulate the thyroid
Clinical features	Hyperthyroidism: - Agitation, tremor & sleep disturbance - Heat intolerance, Sweating & palpitations - Weight loss (w/increased appetite) - Goiter - Ophthalmopathy - Muscle weakness



Insulin-Dependent Diabetes Mellitus (Type I)

IDDM

Pathophysiology	Type IV (Delayed-Type) Hypersensitivity Autoreactive T-cells invade pancreatic islets and destroy the β (insulin-secreting) cells Macrophages are activated → Insulitis (CMI) → Decreased insulin → hyperglycemia
Mechanisms	1- Genetic susceptibility (HLA-DQ alleles) 2- Autoimmunity 3- Environmental factors (Infections: e.g. Coxsackie virus, Echovirus) (recall that this autoimmunity is due to **abnormal expression of MHC II on non-APC cells (β cells)**, which could be induced by viral infections through increased IFNγ production → T cells will destroy the MHC II-expressing β cells) Most likely scenario: Viruses cause mild β cell injury followed by an autoimmune reaction in **HLA-susceptible** people About 10% of Type I IDDM patients are prone to other autoimmune disorders



A normal islet of langerhans containing several cell types (3 demonstrated), each secreting different hormones and expressing different proteins.

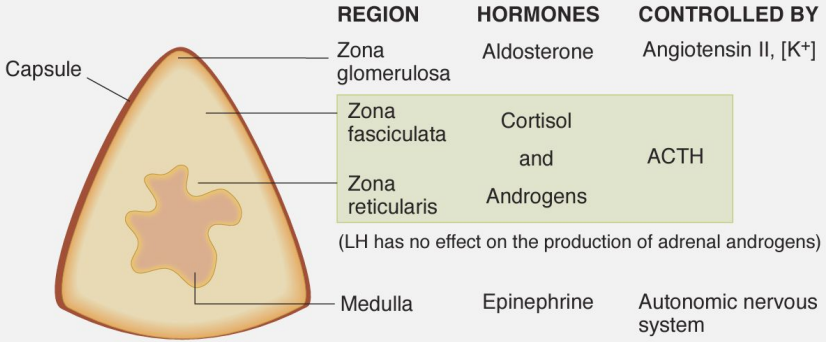
In Type I IDDM, an effector T cell attacks and kills the β cell because it is abnormally expressing MHC peptides.

Insulin can no longer be produced due to the β cell death, while glucagon (α cell) and somatostatin (γ cell) will continue being produced.

Adrenocortical Failure

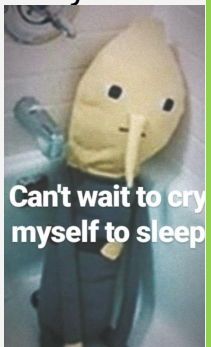
Addison's Disease (prototypical)

Prevalence	M:F ratio is 1:4 Associated with HLA II DR3 and/or DR4 (The most strongly associated DRB1*04 allele is DRB1*04:04)
Pathophysiology	Autoimmune destruction of steroid-producing cells in the adrenal gland A major autoantigen is 21-hydroxylase (21OH), involved in the biosynthesis of cortisol & aldosterone in the cortex T cell-mediated injury is likely to be central to pathogenesis (21 Hydroxylase-specific Cytotoxic T cells) Adrenal autoantibodies **may** have a pathogenic role (unclear yet) or could arise secondary to T-cell tissue damage
Clinical features	Adrenal Insufficiency: - Weakness - Weight loss (w/poor appetite) - Confusion - Shock - **Hyperpigmentation** (underarm) - Hypotension - Weak pulses



Damage to the adrenal cortex may be caused by:

- Autoimmune disease
- Infections
- Hemorrhage
- Tumors
- Use of drugs (anticoagulants)



Quiz:

1. Which one of the following HLA genes is a predisposition for type 1 diabetes mellitus?

a) HLA DR4
b) HLA DR3
c) HLA DQ
d) HLA B1

2. Which one of the following HLA genes is a predisposition for Hashimoto?

a) HLA DR3
b) HLA DR4
c) HLA DR13
d) HLA DR7

3. What is the most likely pathogenic mechanism for Addison's disease?

a) 21 Hydroxylase deficiency
b) Autoantigen against 21 Hydroxylase
c) Cytotoxic attack in the adrenal medulla
d) Destruction in the adrenal cortex

4. What autoimmune endocrine disorder is mediated by both humoral and cell-mediated immunities?

a) Graves disease
b) Chronic Lymphocytic Thyroiditis
c) Systemic Lupus Erythematosus
d) Multiple Sclerosis

5. What type of hypersensitivity is associated with IDDM?

a) Type I
b) Type II
c) Type III
d) Type IV

6. Which of the following plays a protective role in Hashimoto's Thyroiditis?

a) HLA DR4
b) HLA DR7
c) HLA DR13
d) HLA B8

1.C 2.B 3.D 4.B 5.D 6.C

Done by: Ibrahim Aldakhil

Edited by: Abdulrahman Alhawas

Special thanks to: Mohammed A. Alshehri and Meshari Alzeer

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