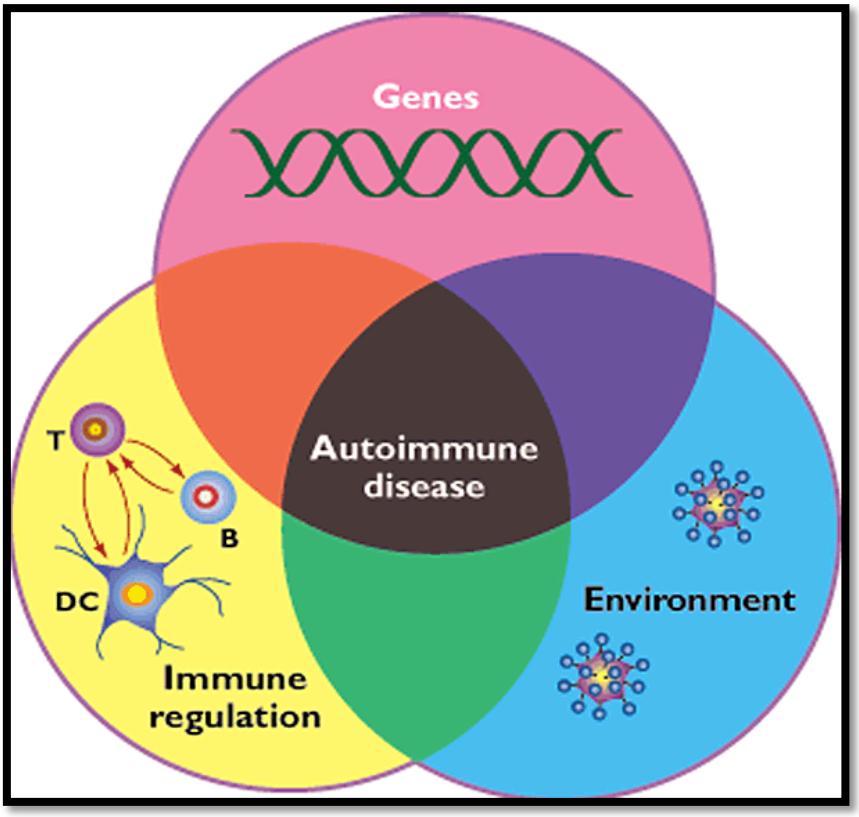
2nd Year

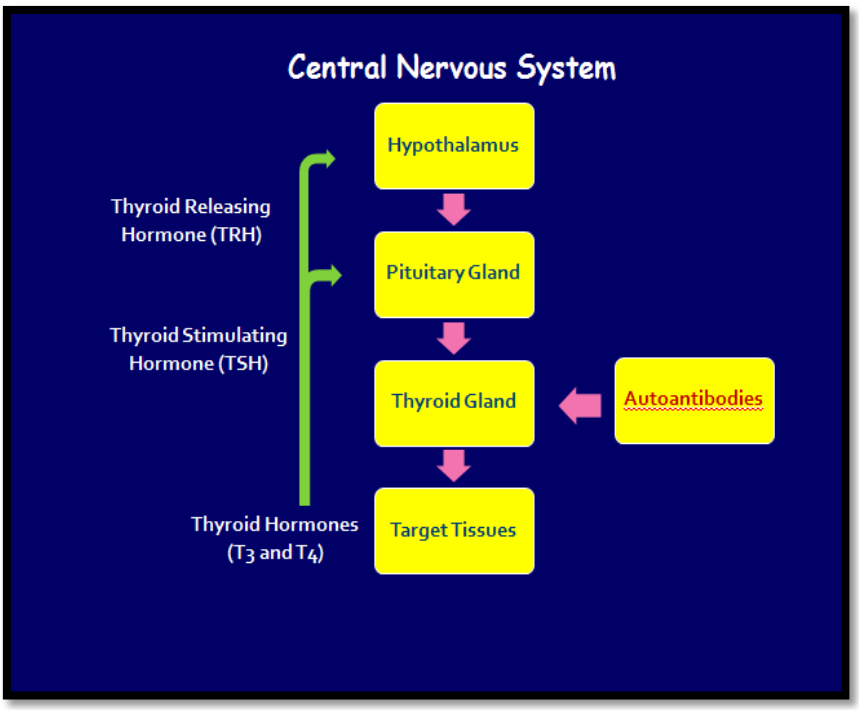
Endocrine Block

Immunology

The Immune System and Endocrine Disorders

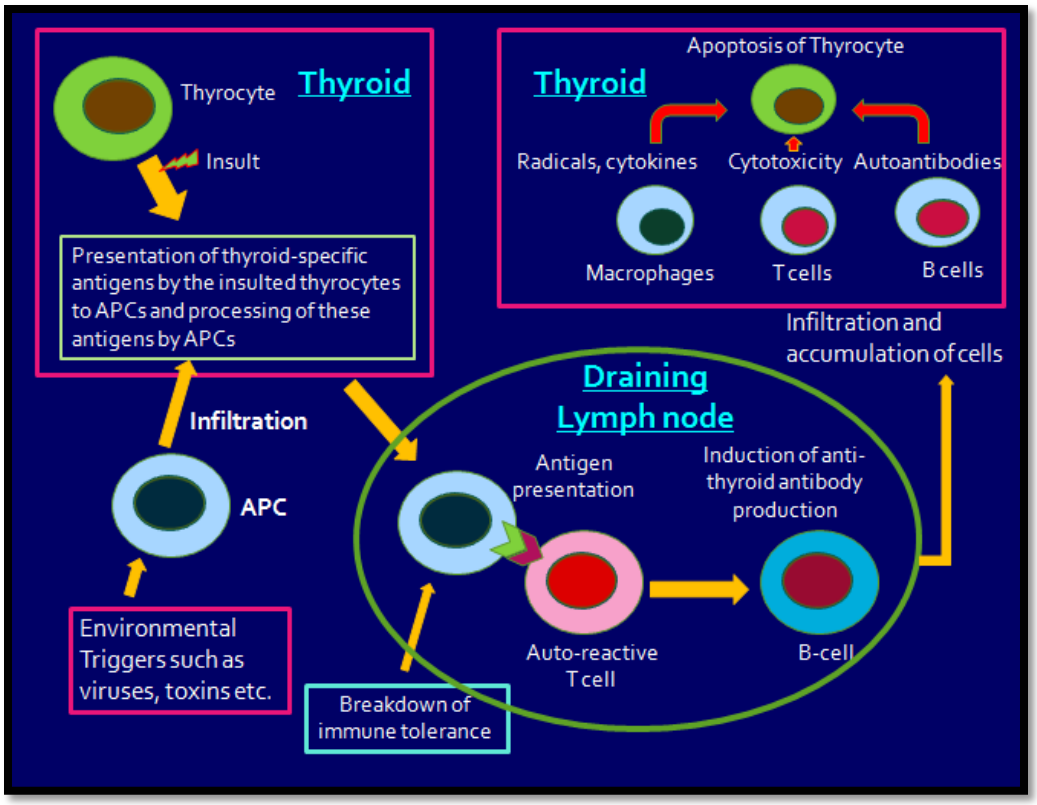
Hadeel AlSajjan





Normal thyroid hormone regulation

The Thyroid and Immune diseases



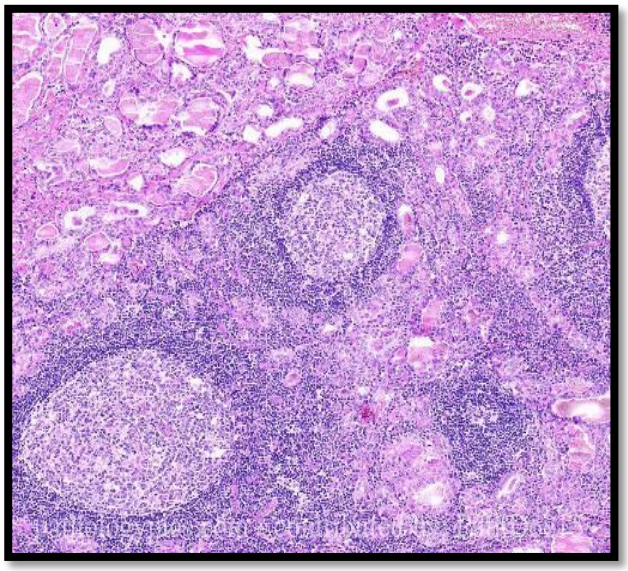
Environmental triggers such as viruses, toxins → Damage to the thyroid tissue (Thyrocyes) → Thyroid antigens are released → APC (Antigen Presenting Cell) takes antigen & presents it to the immune system in the draining lymph nodes → Activation of T-Cells → Activation of B-Cells → Anti-thyroid Antibody production → Other immune component are activated (Radicals, Cytokines, Cytotoxic T-Cells, Macrophages) → Thyrocyte injury. (Thyrocyte Apoptosis)

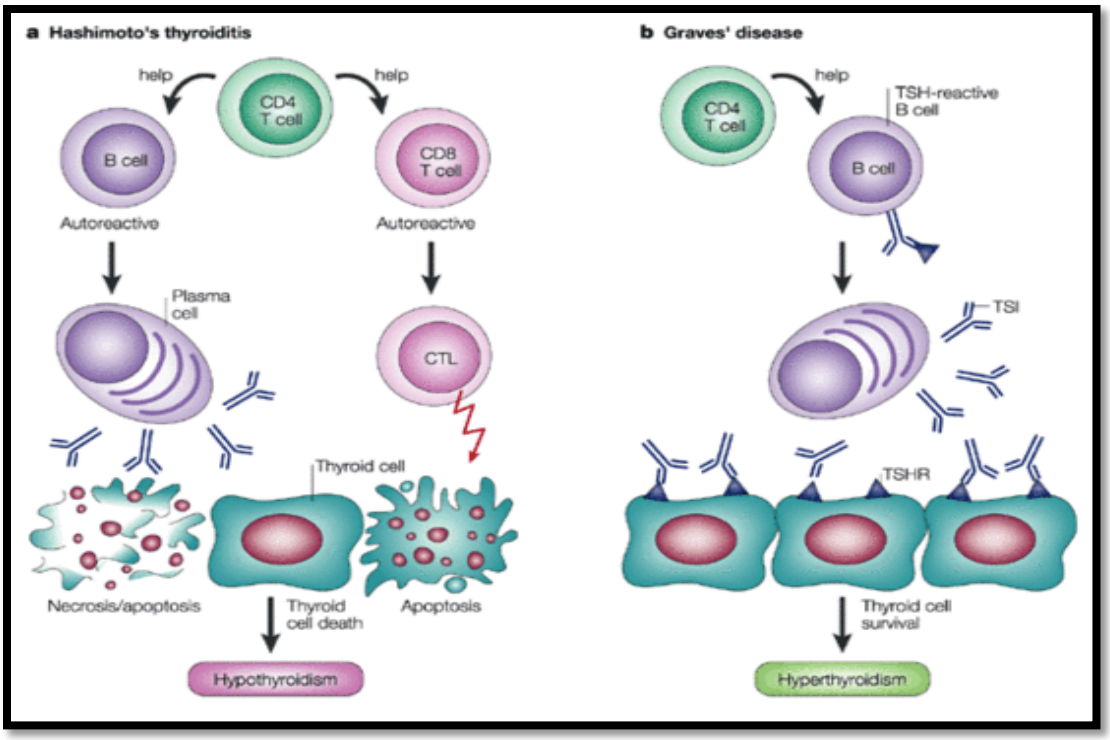
Thyroid

Thyroid Gland (Autoimmune Diseases)

1. Graves' Disease
2. Hashimoto's Thyroiditis

Hashimoto's Thyroiditis





Hashimoto's

- Helper T-Cells (CD 4) produce signals
  - -Activated B-Cells (Plasma Cells) produce antibodies that destroy thyrocytes
  - -Cytotoxic T-Cells (CD 8) Cause thyroid injury
- Damage to the thyrocytes leads to Hypothyroidism

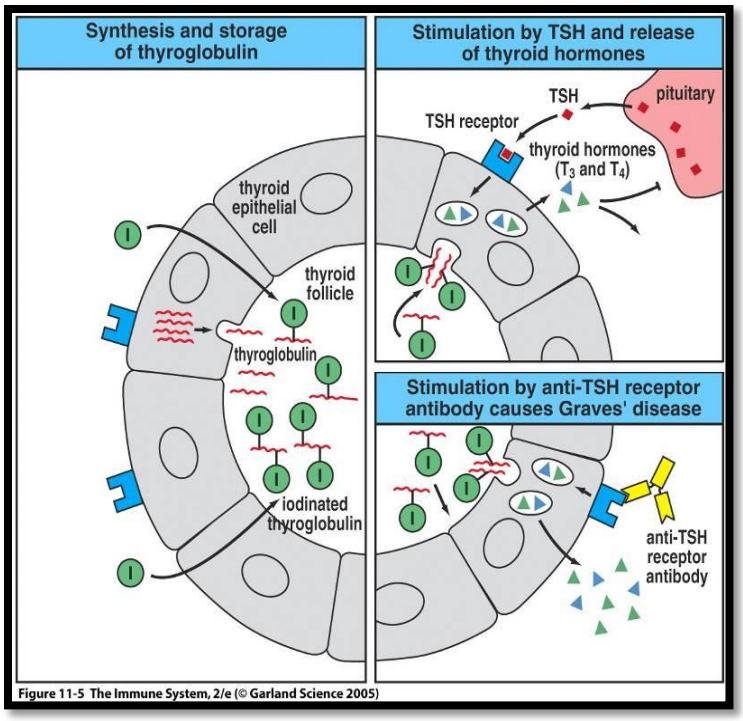
Graves'

- Helper T-Cells (CD 4) produce signals
- Activated B-Cells produce Anti TSH antibodies
- Antibodies bind to TSH receptors on thyroid gland
- Causing over production of thyroid hormones
- Leading to Hyperthyroidism

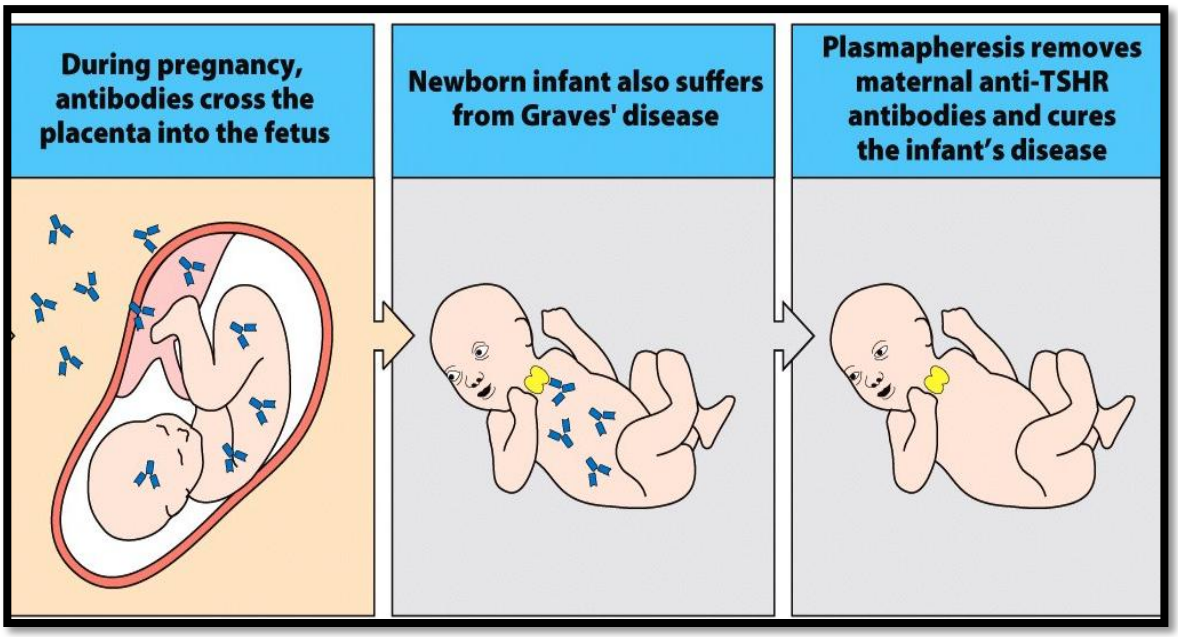
Graves' Disease

Anti Thyroid Antibodies

- Graves' Disease (Hyperthyroidism)
- Thyroid Stimulating Immunoglobulin (TSH receptor antibodies)
  - -Binds and activates TSH receptor in Thyroid
  - -Seen in Hyperthyroidism: Grave's Disease



Mother with Graves' disease makes thyroid stimulating hormone receptor antibodies



- Baby is born with Hyperthyroidism
- The antibodies could disappear on their own as the baby's immune system develops.
- If not, then plasmapheresis is used to get rid of them.

Hashimoto's Thyroiditis

Hashimoto's thyroiditis

- Anti-thyroid Microsomal Antibody (Tissue destruction and blocking antibodies)
    - Present in Hypothyroidism
        - Hashimoto's thyroiditis

- Anti-thyroglobulin Antibody
    - Seen in Hashimoto's Thyroiditis
    - Less commonly elevated compared with thyroid microsomal antibody

Antibodies found in Hashimoto's
- Anti-thyroid Microsomal Antibody (Commonest)
- Anti-thyroglobulin Antibody (Less Common)

Anti Microsomal Antibodies

- Microsomes are found inside thyroid cells
- The body produces antibodies to microsomes when there has been damage to thyroid cells

Alternative Names

- Thyroid anti-microsomal antibody
- Anti-microsomal antibody
- Microsomal antibody
- Thyroid peroxidase antibody (TPOAb)

Anti Microsomal Antibodies

- The thyroid microsomal antigen has been shown to be the enzyme thyroid peroxidase (TPO)
- TPO is a membrane-bound enzyme and plays a significant role in the biosynthesis of thyroid hormones
- Autoantibodies produced against TPO are capable of inhibiting the enzyme activity
- Antibodies to TPO have also been found in:
    - More than 90% patients with autoimmune thyroiditis (Hashimoto's thyroiditis)
    - 50% of patients with Graves' disease (This is why some patients who suffer from graves' may have episodes of hypothyroidism)
    - Less frequently in patients with other thyroid disorders
- Low titers may also be found in 5-10 percent of normal individuals

Hashimoto's Continued

Anti Thyroglobulin Antibodies

- Thyroglobulin Antibodies are directed against the glycoprotein thyroglobulin located in the thyroid follicles
- 90 percent of patients with Hashimoto's thyroiditis have thyroglobulin or thyroid microsomal antibodies

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Pancreas
Type I Diabetes mellitus

Type 1 Diabetes mellitus

- Autoimmune destruction of the beta cells in the pancreas which produce insulin
- Requires insulin administration for controlling high blood sugar levels

Predisposition

- Genetic (HLA DRB, DQA, DQB)
- Viral infections
- Stress
- Environmental exposure - exposure to certain chemicals or drugs

❖ Immunological destruction of beta cells of pancreas
❖ 10% chance of inheriting if first-degree relative has diabetes
❖ Most likely to inherit from father

Viruses

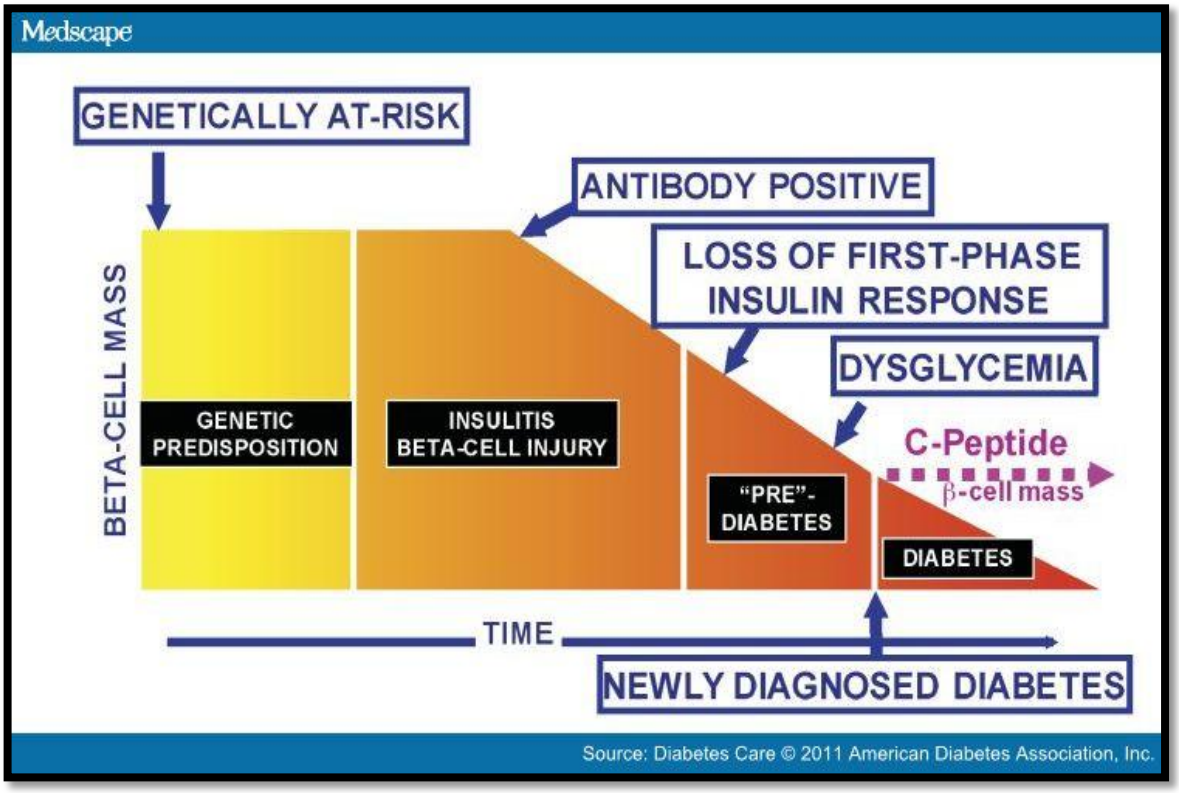
Infection introduces a viral protein that resembles a beta cell protein
Cross-reacting T-cells and antibodies because of molecular mimicry attack beta cell proteins and virus

> Virus is close to Pancreatic B-cells in structure (They both have a similar protein) → Immune system mistakes B-cells for pathogen → Attacks B-Cells → Destruction of B-cells

Cow's milk

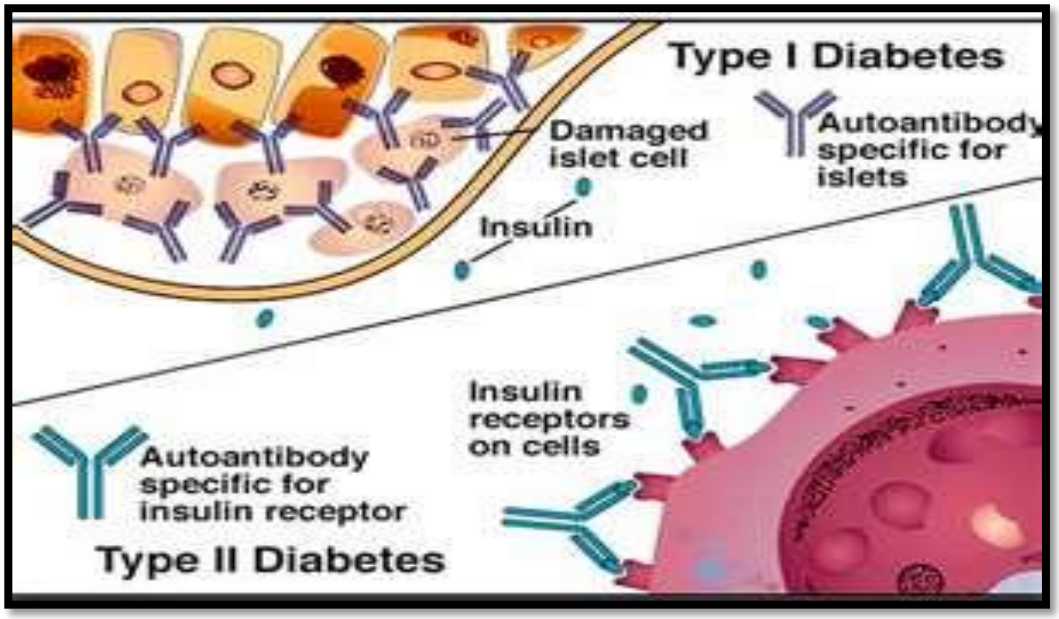
Certain protein which may trigger attack on beta cells (molecular mimicry)

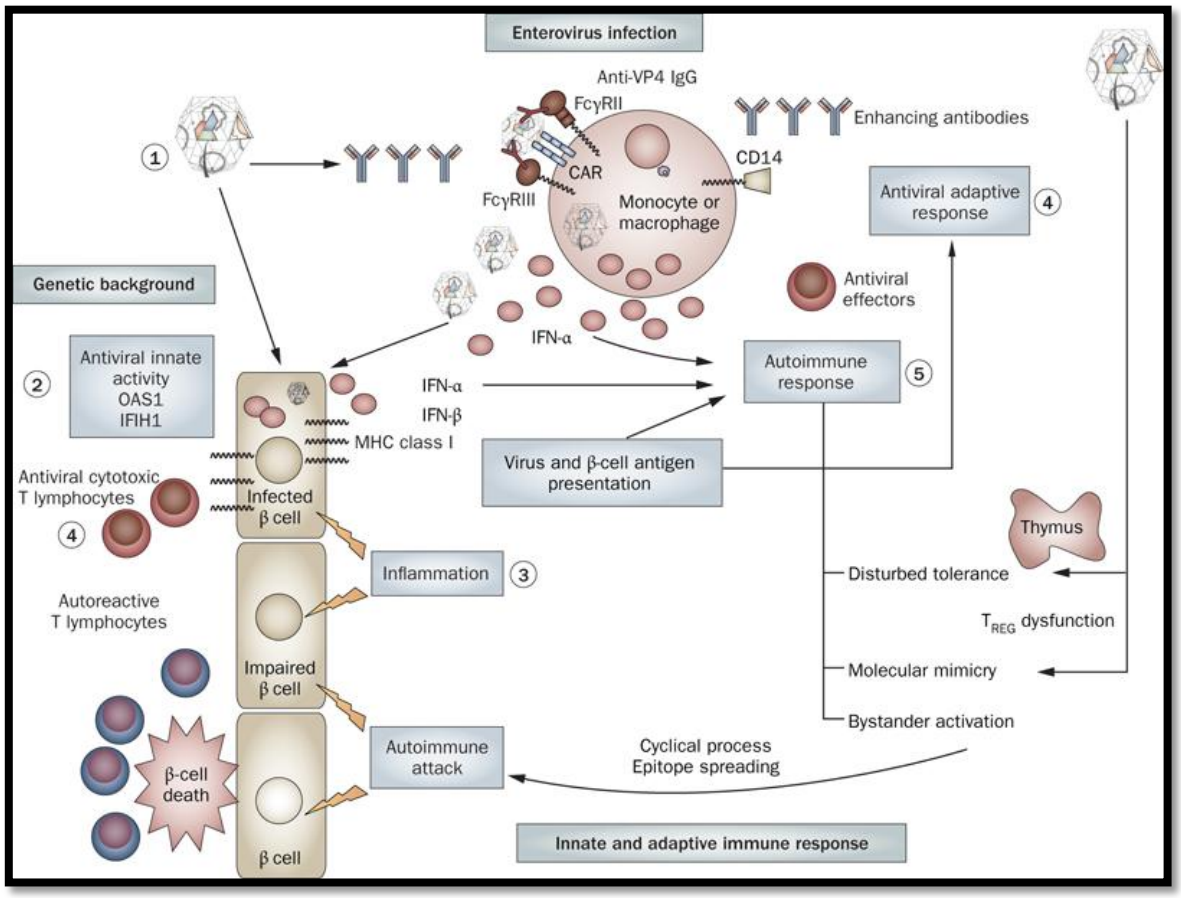
Development of Type I diabetes mellitus



Destruction of B-cells → Starts with hyperinsulinemia (Due to massive primary release of insulin post B-cell destruction) → however, it soon turns into hypoinsulinemia (Complete B-Cell destruction → No more insulin syntheses) → Hyperglycemia (Type 1 diabetes)

Immunological damage in diabetes





- Viral infection → Molecular mimicry → B-cell destruction
- Both the Innate and Adaptive immunity play a role in the development of Type 1 Diabetes

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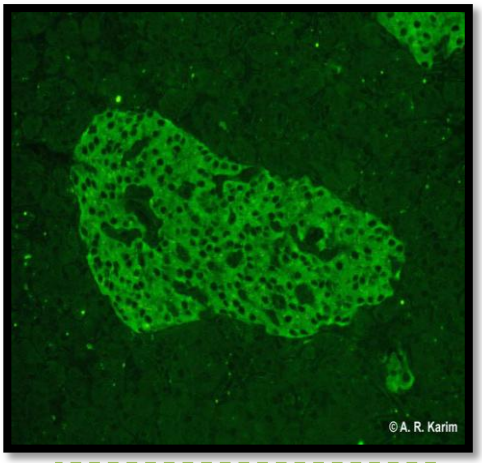
Diabetes

Four autoantibodies are markers of beta cell autoimmunity in type 1 diabetes:

- Islet Cell Antibodies (ICA), against cytoplasmic proteins in the beta cell found in 75-90% patients
- Antibodies to Glutamic Acid Decarboxylase 65 (GAD65) in 80% of patients
- Insulin Auto-antibodies (IAA) is the first marker found in 70% of children at the time of diagnosis
- IA-2A, to protein tyrosine phosphatase found in 54-75% of patients



Islet cell antibody (Immunofluorescence)

Differential Diagnosis

- Type 1 diabetes may be diagnosed by the presence of one or more auto-antibodies
- People who screen positive for one or more auto-antibodies may ***not*** necessarily develop diabetes
- Risk of having type 1 diabetes is proportional to titer of antibodies

Interpretation

- Antibodies may be present several years before a patient develops hyperglycemia
- Presence of auto-antibodies impair insulin response

Limitations

- Auto-antibodies may disappear months or years later without the development of diabetes
- Since insulin-treated patients develop insulin antibodies, analysis of IAA is not useful in insulin-treated patients
- Antibodies may be transferred trans-placentally to infants of type 1 diabetic mothers so caution must be used for interpretation

Anti-insulin antibodies

Anti-insulin antibodies either of IgG and/or IgM class against insulin are elevated and this may make insulin less effective or neutralize it

- **IgG**: is the most common type of anti-insulin antibody
- **IgM**: may cause insulin resistance
- **IgE**: may be responsible for allergic reactions

Disease associations

About 10% patients with Type 1 diabetes are prone to other autoimmune disorders such as:

- Graves' disease
- Hashimoto's thyroiditis
- Addison's disease
- Pernicious anemia

Adrenals
Autoimmune adrenocortical failure
Addison's disease

Addison's disease

- It develops as a consequence of autoimmune destruction of steroid-producing cells in the adrenal gland
- 75 to 80% of all cases of adrenal insufficiency or Addison's disease are of autoimmune origin with circulating anti-adrenal antibodies
- The damage is probably mediated by T cells and the role of antibodies is unclear

Adrenal antibodies

- Adrenal antibodies are also known as adrenocortical antibodies (ACA)
- Antibody to 21-Hydroxylase an enzyme involved in biosynthesis of cortisol and aldosterone is the best marker of autoimmune Addison's disease,
- Other antibodies rarely tested are:
  - 17 alpha hydroxylase
  - Cytochrome P450

- Graves' disease is caused by stimulating antibodies
- Hashimoto's thyroiditis is associated with tissue damage mediated by proinflammatory cells and antibodies directed to self antigens in thyroid gland
- Type I diabetes mellitus results from immune mediated destruction of beta cells in pancreas and a number of auto-antibodies can be detected in patients
- In majority of patients with Addison's disease evidence of auto-immunity can be detected by the presence of anti-adrenal antibodies