MED 443
King Saud University

443
IMMUNOLOGY TEAM

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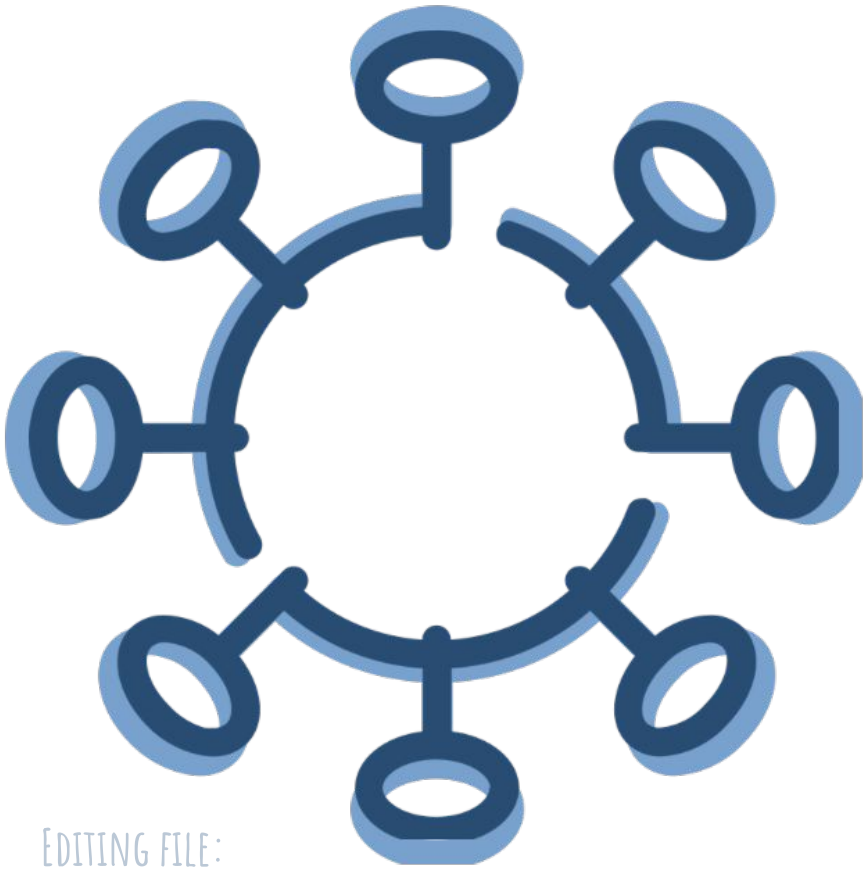
The Immune System and Endocrine Disorders

ENDOCRINE BLOCK



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.

LECTURE WAS PRESENTED BY DR.REEM SGHIRI AND PROF.ADEL ALMOGREN

REFERENCE: KUBY IMMUNOLOGY 7TH EDITION 2013 CHAPTER 16 PAGES 526-527 (FROM FEMALE SLIDES)
KUBY IMMUNOLOGY 8TH EDITION 2019 CHAPTER 16 (FROM MALE SLIDES)

PLAYLIST (OSMOSIS+NINJA+ARMANDO)

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COLOR INDEX

- MAIN TEXT
- FEMALE SLIDES
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Introduction

Organ- specific

Focusing in one organ

➥ Many endocrine disorders are **organ-specific autoimmune diseases.**
➥ In organ-specific autoimmune disease, the immune response is directed to a **target antigen unique to a single organ.**
➥ the manifestations are largely **limited** to that organ.
➥ The damage may be directly mediated by: Graves is an organ specific disease

1. **Humoral** (Antibodies) Immunity the antibodies may **Overstimulate** **or** **Block** the normal function of the target organ.
2. Cell-mediated Immunity (**CMI**).
3. In some cases **BOTH are involved.**

في الأغلب يكونون الأثنين مع بعض

Immune recall

EXTRA

IF YOU WANT AN IMMUNOLOGY RECAP FORM FIRST YEAR CLICK HERE

Examples of Autoimmune endocrine diseases

Targeted by immunity in Female

Thyroid	
Hashimoto's Disease	Autoantibodies against thyroid peroxidase and thyroglobulin.
Primary Myxoedema	Atrophy of the Thyroid. (Also known as atrophic thyroiditis)
Graves' Disease	Autoantibodies against Thyroid Stimulating Hormone receptor (TSH-R) Autoimmune disease
Pancreas	
Type I diabetes	Autoreactive T-cells invade the pancreatic islets
Adrenal	
Addison's Disease	Chronic endocrine disorder; adrenal glands produce insufficient steroid hormones
Gonads	
Autoimmune Oophoritis	inflammation of the ovaries.
Autoimmune Orchitis	Testicular pain involving swelling, inflammation and infection.
Pituitary	
Lymphocytic Hypophysitis	Low production of one or more hormones by the pituitary gland due to autoantibodies and autoimmunity

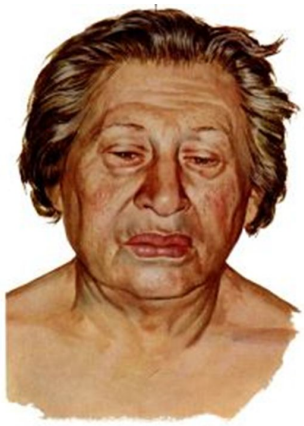
Thyroid Autoimmunity

Hypothyroidism	Hyperthyroidism
● Hashimoto's Disease ● Atrophic Thyroiditis	● Graves' Disease

Chronic lymphocytic thyroiditis (Hashimoto's Thyroiditis)

Epidemiology

- Male:Female ratio is 1:3 most of autoimmune diseases are common in female
- Frequently seen in **middle-aged women**
- Associated with **HLA II**
- Predisposing effect: **DR4** شفناه فيه RA
- Protective role: **DR13**
- There will be symptoms of **hypothyroidism**

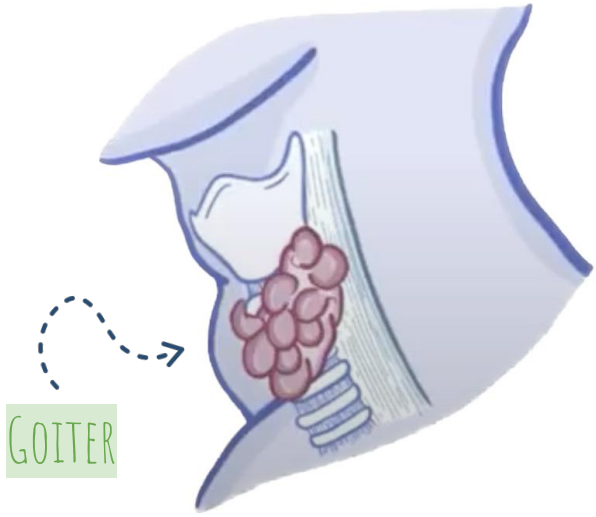


- **Auto-Antibodies** found:

- Anti-thyroid peroxidase
- Anti-thyroglobulin antibodies.

Clinical features

1. Fatigue ,Loss of energy
2. Cold intolerance
3. Weight gain
4. Mental slowing
5. Enlarged thyroid (Goiter)



Chronic lymphocytic thyroiditis (Hashimoto's Thyroiditis)

Features:

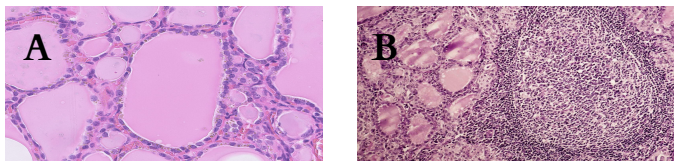
- Production of **Auto-Antibodies**
- Sensitization of TH1 (Mediates inflammation) cells specific for thyroid antigens

1- the DTH* (type IV) response

*Delayed type hypersensitivity

➥Characterized by an intense infiltration of the thyroid gland by
○ Lymphocytes ○ Macrophages ○ Plasma cells
➥Which form **Lymphocytic follicles** & **Germinal centers**

Normal/Abnormal Thyroid



(A) Normal thyroid gland showing a follicle lined by cuboidal follicular epithelial cells

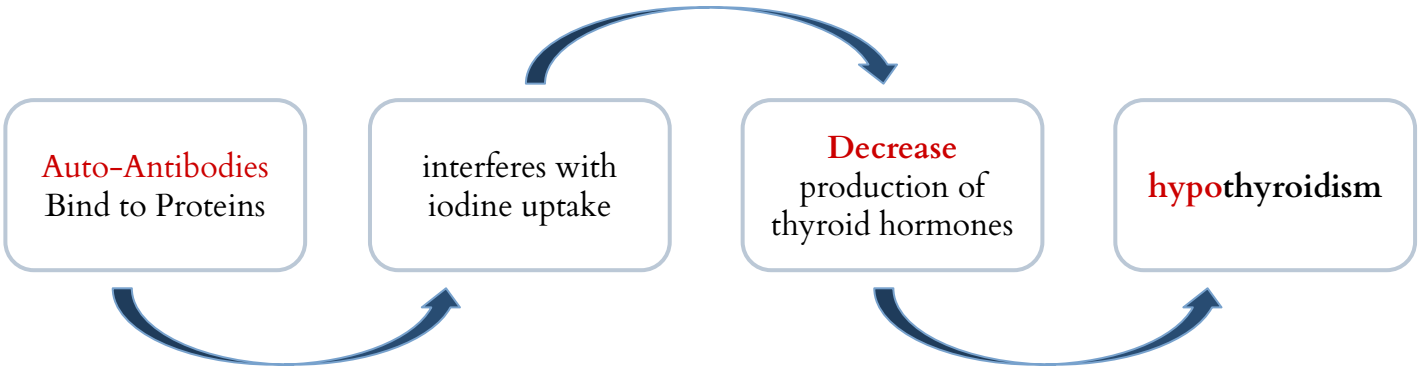
(B) Hashimoto's thyroiditis showing intense lymphocyte infiltration

2- the Inflammatory response causes:

1- Goiter (Physiological response to hypothyroidism)
2- Formation of Antibodies to thyroid proteins. e.g:
- **Thyroglobulin Antibodies**
- **Thyroid peroxidase Antibodies**

"Both are involved in the uptake of Iodine"

Why do goiter occurs? Because gland try to compensate the hypothyroidism

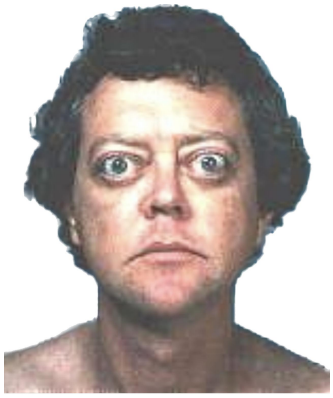


Graves disease

Less common than Hashimoto's disease

Epidemiology

- Male:Female ratio is **1:7**
- Associated with **HLA II**
- Predisposing effect: **DR3**
- Protective role: **DR7**
- There will be symptoms of **hyperthyroidism**

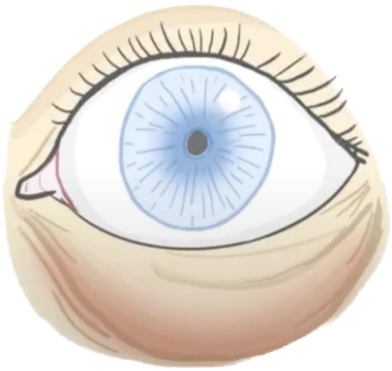


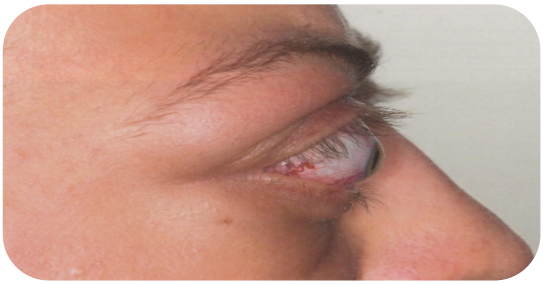
- **Auto-Antibodies** found:

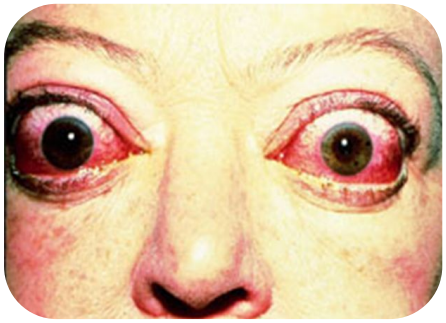
- Long-acting thyroid-stimulating (LATS) antibodies

Clinical features

- Agitation & sleep disturbance
- Sweating
- Palpitations
- Muscle weakness
- Weight loss despite increased appetite
- **Goiter**
- Tremor
- **Ophthalmopathy**, Photos below







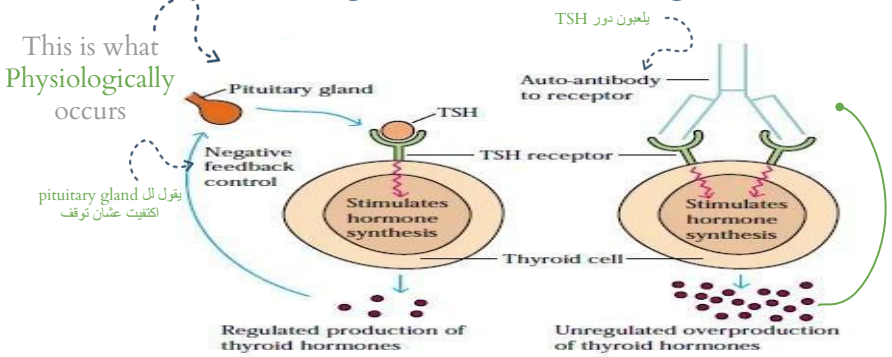
Extra: cause of exophthalmos

Fibroblast in the tissue around eyes + in skin get stimulated by thyroid stimulating antibodies→ make extracellular matrix proteins (Glycosaminoglycans)→Build up over time→Exophthalmos

Graves disease

Normal Vs Graves

Stimulating Autoantibodies (graves Disease)



In graves disease, binding of autoantibodies to the receptor for TSH induces unregulated activation of the thyroid, leading to overproduction of TH (purple dots)

Normal

➥The production of thyroid hormone is regulated by TSH which is produced by the pituitary gland

➥ Binding of TSH to receptor on thyroid cells results in:

- Activation of adenylate cyclase
- Stimulating the synthesis of T4 & T3

Graves

➥ Auto-antibodies bind to the receptor for TSH

➥ Mimicking TSH normal action

➥ Activating adenylate cyclase

➥ Production of the thyroid hormones

Unlike TSH

➥ the autoantibodies are not regulated, and consequently they overstimulate the thyroid.

➥ For this reason these auto-antibodies are called:

Long-acting thyroid-stimulating (LATS) antibodies

No negative feedback

Q) Now you know the pathophysiology would you classify this as molecular mimicry?
A) No, Why? well in molecular mimicry its caused by an antibody that's secreted to a foreign body that cross reacted with a cell but in this case the antibodies that were secreted were designated for the TSH receptors itself, that's why it's not classified as molecular mimicry.

Insulin-dependent diabetes mellitus (IDDM)

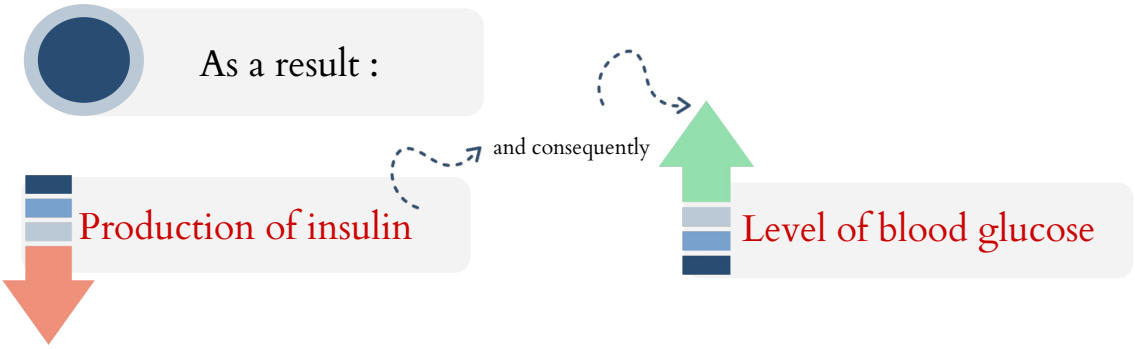
Pathogenesis:

IDDM is an example of Type IV hypersensitivity reaction:

Delayed Hypersensitivity reaction

- Autoreactive **T-cells** invade the pancreatic islets
- Destroy the **insulin-secreting beta cells**
- Macrophages become activated by IFN-γ
- This is frequently referred to as **Insulitis.** (**Cell-mediated DTH response**)

Inflammation in the islets



type 1 Diabetes mellitus (DM1):

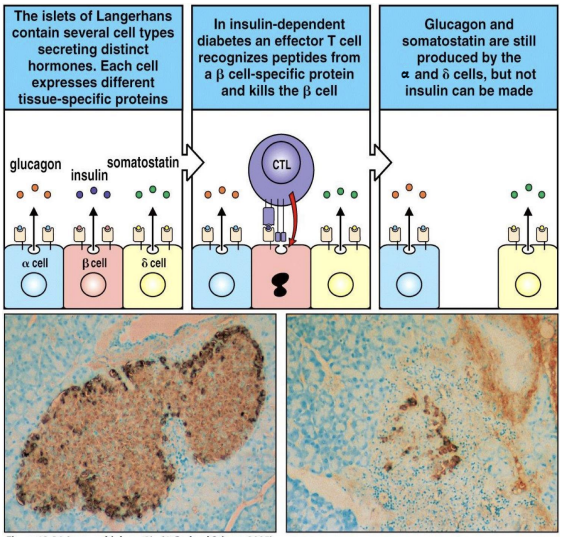
Pathogenesis: three mechanisms responsible for the islet cell destruction:

- Genetic susceptibility **(HLA-DQ alleles)**
- Autoimmunity
- Environmental factors. Infections :
  - Coxsackie virus??
  - Echovirus??

How can we link between this virus and the disease? It's based on **epidemiology** studies

Insulin-dependent diabetes mellitus (IDDM)

Type 1 insulin-dependent diabetes



Cytotoxic T cells will destroy the islets

Pancreatic **β** cells autoreactive T-cells (DTH & CTL) and autoantibodies all play a role in the cellular destruction

#436: **β** cells improperly express of class II (remember that **β** cells aren't APCs, so it's abnormal), cell antigens in beta cells then will be presented. T-cells (TH1) will come and attack the **β** cells. What makes **β** cells express abnormal class II MHC? Macrophages, produced IFN-γ which upregulates Class II MHC expression. IFN-γ produced might be triggered by the viral infection.

The most likely scenario:

is that viruses cause mild beta cell injury, which is followed by an autoimmune reaction against altered beta cells in persons with HLA-linked susceptibility.

تحصل عند أشخاص عندهم genetic deposition

Type 1 IDDM patients (aprox.10%) are prone to other autoimmune disorders

type 1DM مو بس

Autoimmune adrenocortical failure (Addison's disease)

It is Prototypical organ–specific autoimmune disorder

OSMOSIS

Addison's Disease - Genetics:

Female: Male ratio: 4:1

most of autoimmune diseases are common in female

Susceptibility genes:

- HLA-DR3 and/or DR4
- The most strongly Associated DRB1*04 allele is DRB1*04:04

Autoimmune adrenocortical failure (Addison's disease)

Pathogenesis:

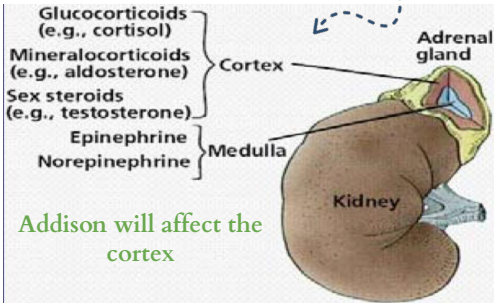
- T cell-mediated injury is likely to be central to pathogenesis
- Adrenal Autoantibodies may have a pathogenic role, as yet unclear, or could arise secondary to T cell-mediated tissue damage. So basically CMI+autoantibodies but we don't know why
- It develops as a consequence of Autoimmune destruction of steroid-producing cells in the adrenal gland
- A major autoantigen is **21-hydroxylase (21OH)**
  - Which is involved in Biosynthesis of cortisol and aldosterone in the adrenal cortex

Extra

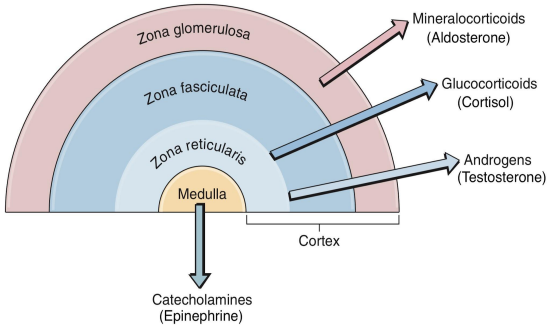
Figure 13.1 An example of increased skin pigmentation in an individual with Addison's disease (left) and resolution post-treatment (right).

Adrenal Gland:

Hormones of the Adrenal glands

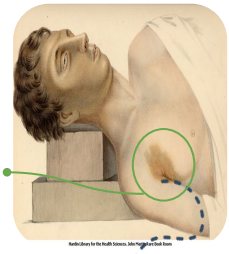


Adrenal cortex



Primary adrenal insufficiency: Symptoms & Physical findings:

- weakness
- weight loss
- poor appetite
- confusion
- hyperpigmentation under arm
- hypotension
- weak pulse
- shock



Addison ← لازم نفكر ؟ Hyperpigmentation

Damage to the Adrenal cortex may be caused by:

- **Autoimmune Disease**
- infections
- Hemorrhage
- tumors
- Use of drugs (anticoagulants)

Summary

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REMEMBER	Hashimoto's	Graves'	IDDM	Addison's
Predisposing /Susceptibility	HLA-**DR4**	HLA-**DR3**	HLA-**DQ**	HLA-DR3 and/or DR4
Protective role	HLA-**DR13**	HLA-**DR7** CR7 protect your team from Grave 	-	
Immune effector (Mostly autoantibodies)	TH1 cells **Anti-thyroid peroxidase** autoantibodies **antithyroglobulin** autoantibodies	LATS antibodies (Also Known as TSH-R) when we train LATS you will be dead in the Grave 💀 	TH1 cells **β** islet cell autoantibodies +DTH+CMI	Anti-**21-hydroxylase** autoantibodies
Autoantigen (self antigen/target)	Thyroid proteins and cells	Thyroid-stimulating hormone receptor	Pancreatic beta cells	Steroid-producing adrenal cells (cortex cells)
Hormones affected	↓T3 and ↓T4	↑T3 and ↑T4	↓Insulin	↓Cortisol and ↓aldosterone

REMEMBER	Pathophysiology
Hashimoto's	CMI and humoral immune responses are activated → production of anti-thyroid peroxidase and anti-thyroglobulin → binding of autoantibodies to these proteins → interfere with iodine uptake → decreased production of thyroid hormones → hypothyroidism → **DTH response (Type IV hypersensitivity)**
Graves'	B and T cell-mediated **autoimmunity** → production of stimulating antibody against TSH-receptor → ↑ thyroid function and growth → **hyperthyroidism** and goiter
IDDM	Autoreactive T-cells, cytotoxic T lymphocytes (CTL), invade the pancreatic islets and destroy **β** cells (insulin-secreting cells) → Macrophages are activated, frequently referred to as insulitis → cytokine release including **IFN-γ** and production of **β** islet cell autoantibodies → **Cell-mediated DTH response (Type IV hypersensitivity response)** → hyperglycemia
Addison's	A major autoantigen is 21-hydroxylase (21OH), an enzyme involved in the biosynthesis of **cortisol & aldosterone in the adrenal cortex**. (Marker of Autoimmune Addison Disease: **Anti-21-hydroxylase** autoantibodies). T cell-mediated injury is likely to be central to pathogenesis (21 Hydroxylase-specific Cytotoxic T cells).

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good luck

Special Thanks to 442 Immunology team

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