AUTOIMMUNE DISEASE PART I

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Lecture 5

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Self/Non-self Discrimination

Autoimmunity is a problem of self/non-self discrimination.

- A major task of the immune system is to distinguish self from non self.

- Failure to do so results in immune attacks against cells and organs of the host with the possible onset of

Autoimmune disease

AUTOIMMUNITY

- **5 % to 7% adult affected.**
- **Two third women.**
- **More than 40 human diseases autoimmune in origin.**

AUTOIMMUNE DISEASES

Brain
Multiple Sclerosis
Guillain-Barre Syndrome
Autism

Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

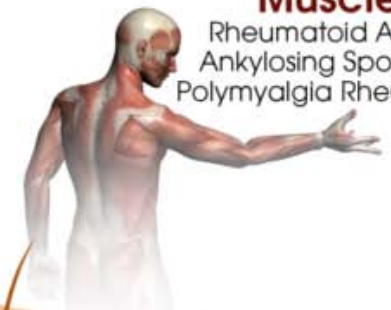
Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia

Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

Over 100
Different Types of AutoImmune Disorders

GI Tract
Celiac's Disease
Crohn's Disease
Ulcerative Colitis
Diabetes Type I

Muscles
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica



Nerves
Peripheral Neuropathy
Diabetic Neuropathy

Skin
Psoriasis
Vitiligo
Eczema
Scleroderma

Lung
Fibromyalgia
Wegener's Granulomatosis

WHAT IS AUTOIMMUNE DISEASE?

AUTOIMMUNITY

Is the failure of an immune system to recognize its own constituent parts as *self*, which allows an immune response against its own cells and tissues

Break of Tolerance

IMMUNE TOLERANCE

- is a state of unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response in given organism.
- It is induced by prior exposure to that specific antigen.

Why is tolerance critical to the normal functioning of the immune system?

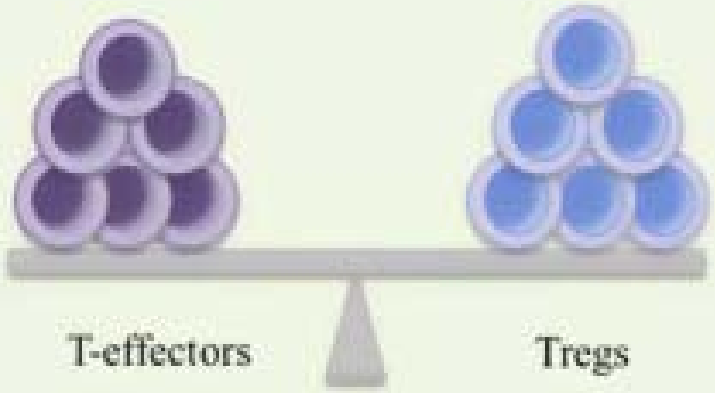
The term **tolerance** applies to the many layers of protection imposed by the immune system to:

- ❑ prevent the reaction of its cells and antibodies against host components.

In other words:

individuals should not typically respond aggressively against their own antigens, although they will respond to pathogens or even cells from another individual of the same species.

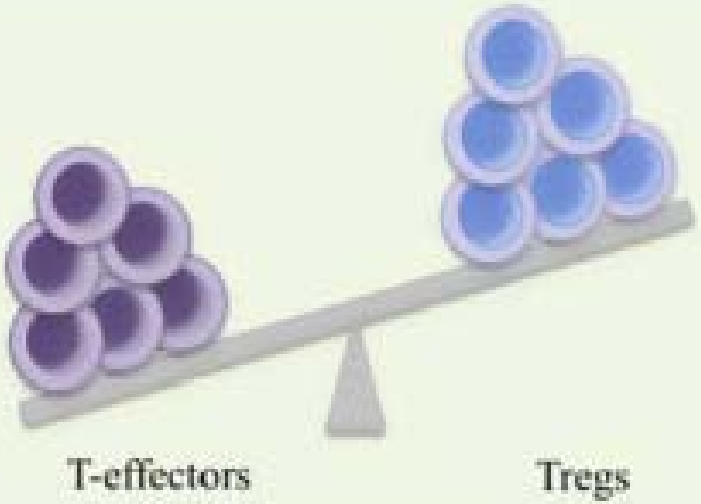
Balanced Immune Responses



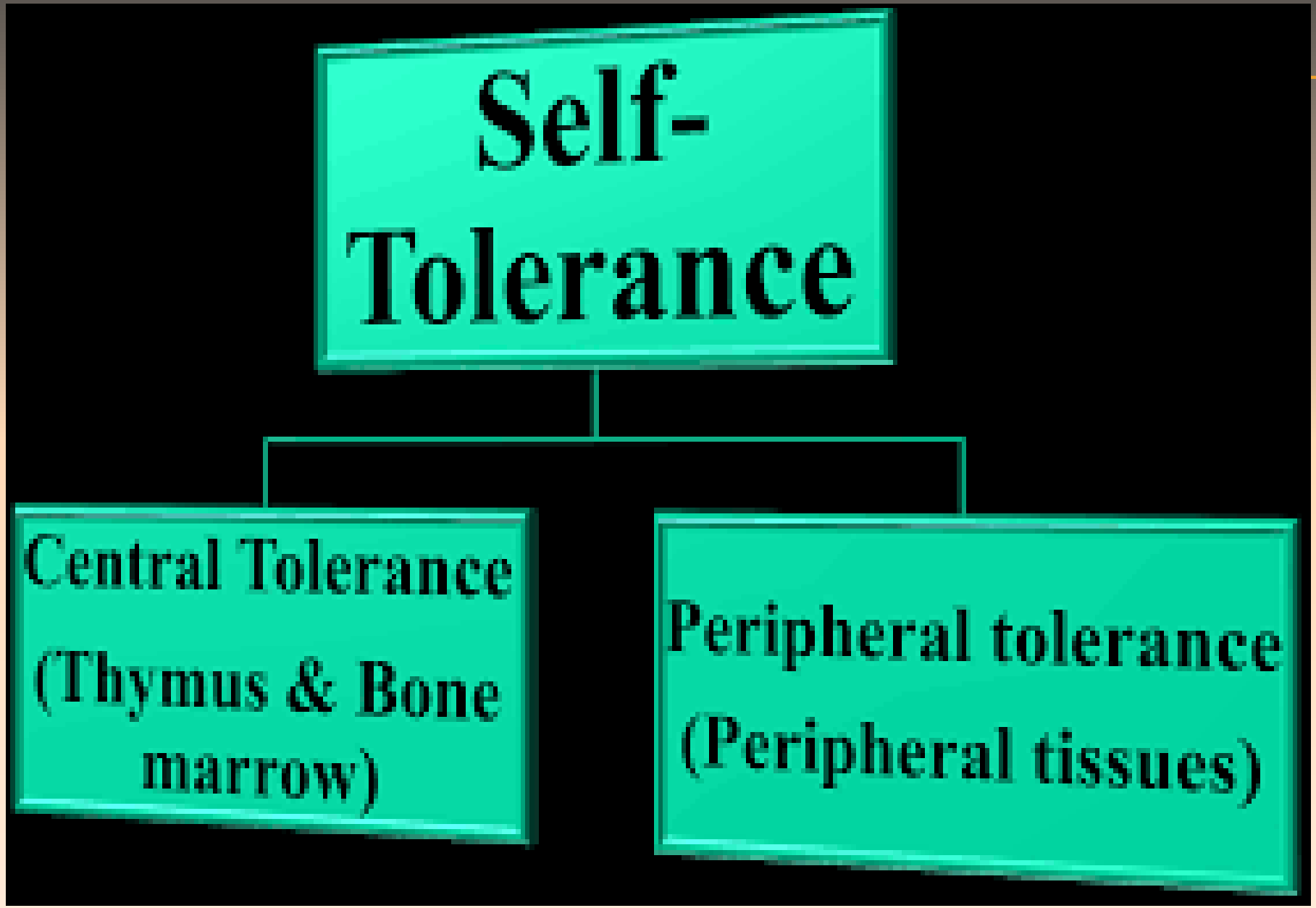
Tolerance

1. Reduced susceptibility to Treg suppression

1. Inadequate number of Tregs
2. Defective Treg function
3. Defective Treg phenotype



Autoimmunity


Self-Tolerance
Central Tolerance (Thymus & Bone marrow)
Peripheral tolerance (Peripheral tissues)

What are the types of tolerance????

I/ central tolerance

In the first step of this process, a phenomenon termed

- **Central tolerance**
- Central tolerance occurs in the primary lymphoid organs: the bone marrow for B cells and the thymus for T cells .

- deletes T- or B-cell clones before the cells are allowed to mature if they possess receptors that recognize self antigens with high affinity .

II/peripheral tolerance

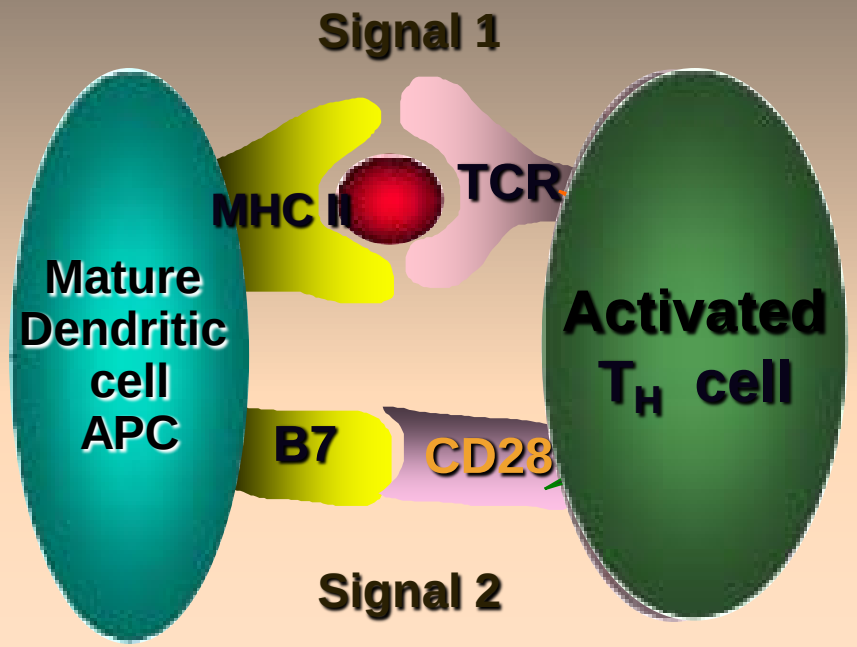
which renders some self-reactive lymphocytes in secondary lymphoid tissues inactive and generates others that actively inhibit immune responses against self . which is regulated by programs that induce cell death (apoptosis) following receipt of specific signals:

1. **Clonal Anergy-failure of APC to deliver a second signal during antigen presentation (example: B7-CD28 interaction).**

2. Suppression of responses may occur by production of regulatory T cells that inhibit immune response to self-antigen (example: TGF-b, IL10 and Th1 vs. Th2 cytokines).

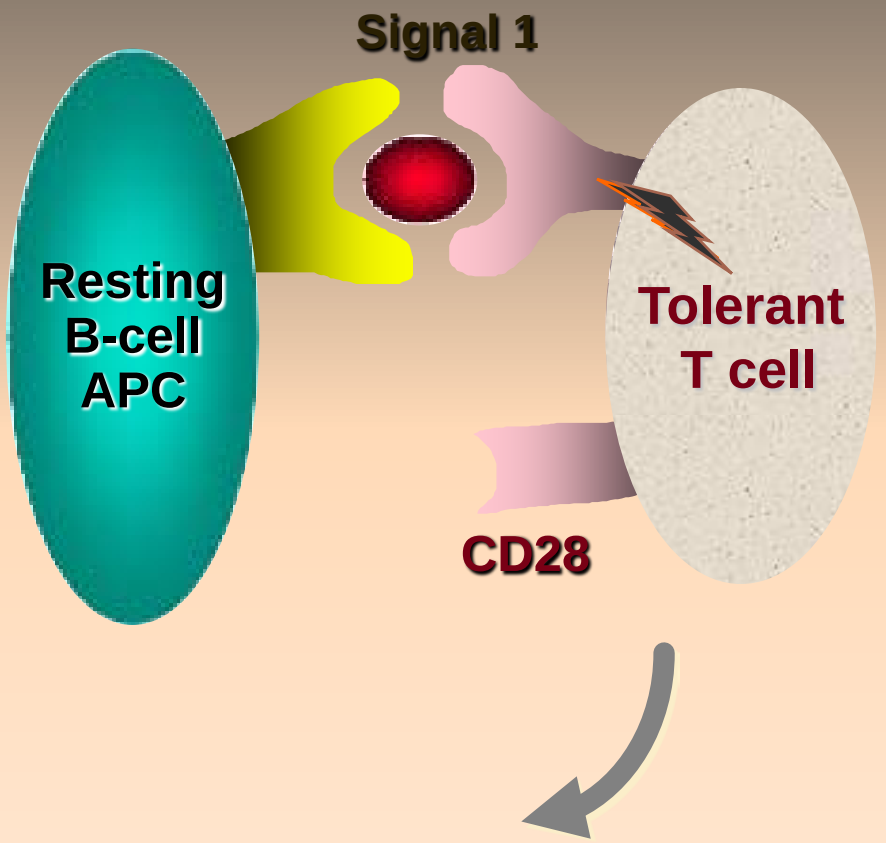
3. Ignorance to some self antigens may also exist

THE TWO SIGNAL HYPOTHESIS FOR T-CELL ACTIVATION



Clonal anergy outside the thymus. **A:** B7 protein on the antigen-presenting cell interacts with CD28 on the helper T cell, and full activation of the helper T cell occurs. **B:** B7 protein on the antigen-presenting cell is not produced; therefore, CD28 on the helper T cell does not give a costimulatory signal. Anergy of the helper T cell occurs despite interaction of the T-cell receptor (TCR) with the epitope

HYPOTHETICAL MECHANISM OF TOLERANCE IN MATURE T CELLS



Tolerance (anergy or apoptosis) from lack of signal 2

The most important step in the production of autoimmune disease is:

1. The activation of self-reactive helper (CD4) T cells.
2. These self-reactive Th-1 or Th-2 cells can induce either:

- Cell-mediated
- Antibody-mediated

Classification

Classification of autoimmune disease

Human autoimmune diseases can be divided into organ specific and systemic diseases

I/ organ Autoimmune diseases:

In an organ-specific autoimmune disease, the immune response is:

- usually directed to a target antigen unique to a single organ or gland, so that the manifestations are largely limited to that organ.
- The cells of the target organs may be damaged directly by humoral or cell mediated effector mechanisms.
- Alternatively, anti-self antibodies antibodies may over stimulate or block the normal function ofthe target organ.

Two types of autoimmune disease

organ-specific

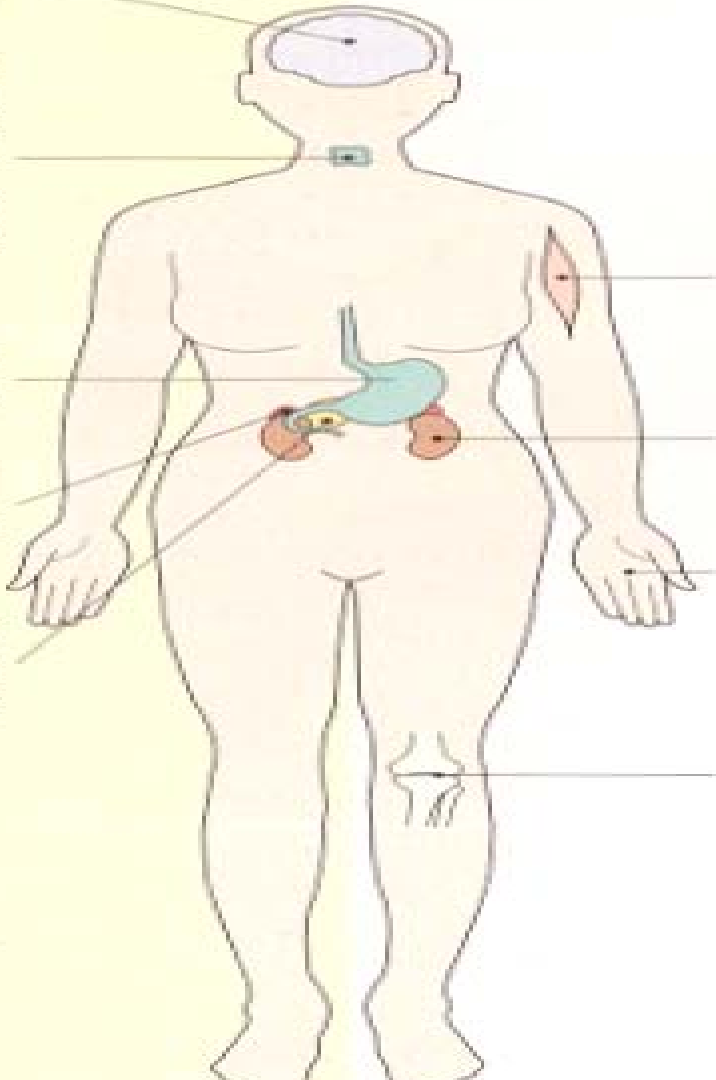
brain
multiple sclerosis(?)

thyroid
Hashimoto's thyroiditis
primary myxoedema
thyrotoxicosis

stomach
pernicious anaemia

adrenal
Addison's disease

pancreas
insulin-dependent diabetes mellitus



non-organ-specific

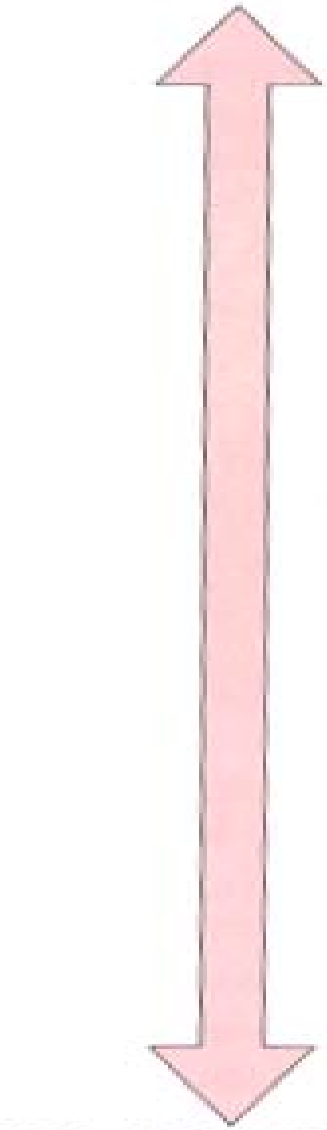
muscle
dermatomyositis

kidney
SLE

skin
scleroderma
SLE

joints
rheumatoid arthritis

The spectrum of autoimmune diseases



Hashimoto's thyroiditis
primary myxoedema
thyrotoxicosis
pernicious anaemia
autoimmune atrophic gastritis
Addison's disease
premature menopause (few cases)
insulin-dependent diabetes mellitus
stiff-man syndrome
Goodpasture's syndrome
myasthenia gravis
male infertility (few cases)
pemphigus vulgaris
pemphigoid
sympathetic ophthalmia
phacogenic uveitis
multiple sclerosis (?)
autoimmune haemolytic anaemia
idiopathic thrombocytopenic purpura
idiopathic leucopenia
primary biliary cirrhosis
active chronic hepatitis (HBsAg negative)
cryptogenic cirrhosis (some cases)
ulcerative colitis
atherosclerosis(?)
Sjögren's syndrome
rheumatoid arthritis
dermatomyositis
scleroderma
mixed connective tissue disease
anti-phospholipid syndrome
discoid lupus erythematosus
systemic lupus erythematosus (SLE)

II/ systemic autoimmune diseases

In systemic autoimmune diseases, the immune response is :

- directed toward a broad range of target antigens and involves a number of organs and tissues.
- These diseases reflect a general defect in immune regulation that results in hyperactive T cells and/or B cells.
- Tissue damage is typically widespread, both from cell-mediated immune responses and from directcellular damage caused by auto-antibodies or by accumulation of immune complexes.

CAUSES OF AUTOIMMUNITY

Death to Diabetes

Autoimmune Disease Root Causes

Autoimmune Disease Root Causes & Risk Factors

Death to Diabetes

- Infections
- Pathogens
  Bacteria, Virus, Fungi, Parasites
- Other Diseases
- Food Intolerance
  Gluten, Grains, Dairy, Soy
- Oxidative Stress
- Chronic Inflammation
- Leaky Gut Syndrome
- Nutrient Deficiencies
- Vaccines (Immunizations)
- **Autoimmune System Dysfunction**
- Environmental Toxins
- Chronic Stress/ Psychological Factors
- Hormonal Imbalances
- Lifestyle, Trauma/ Surgery Events
- Genetics, Gender, Age, Ethnicity
- Thyroid, Other Glandular Dysfunctions
- Medical/Dental Practices
- Weakened Immunity
- Prescription/ OTC Drugs
- Tobacco, Alcohol, Other Drugs

1) Release of sequestered Ag

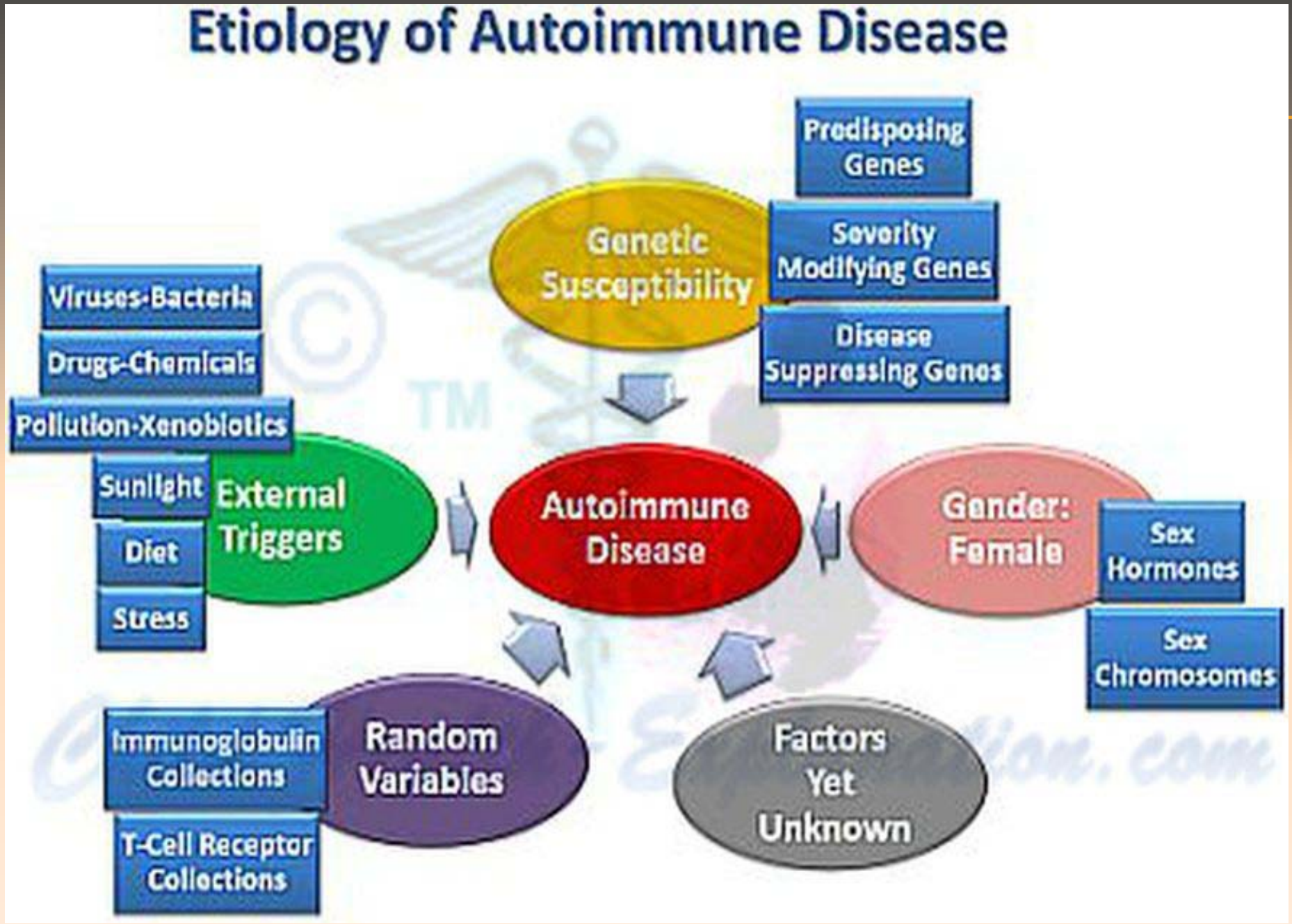
- Smoking can trigger Goodpasture's syndrome
- Alveolar basement membrane normally not exposed to immune system
- Smoking damages alveoli, exposes collagen
- Anti-collagen Ag damages lung and kidney
- Anti-sperm Ab produced in some men after vasectomy
- Injection of myelin basic protein (MBP) produces MS-like EAE
- in mice May be triggered by injury or infection

2) Immune stimulation

- **Microbial infection stimulates APCs carrying self Ag**
- **High level of APCs with “second signal” breaks anergy**

Etiology

Etiology of Autoimmune Disease



There are many factors contributing to autoimmune disease

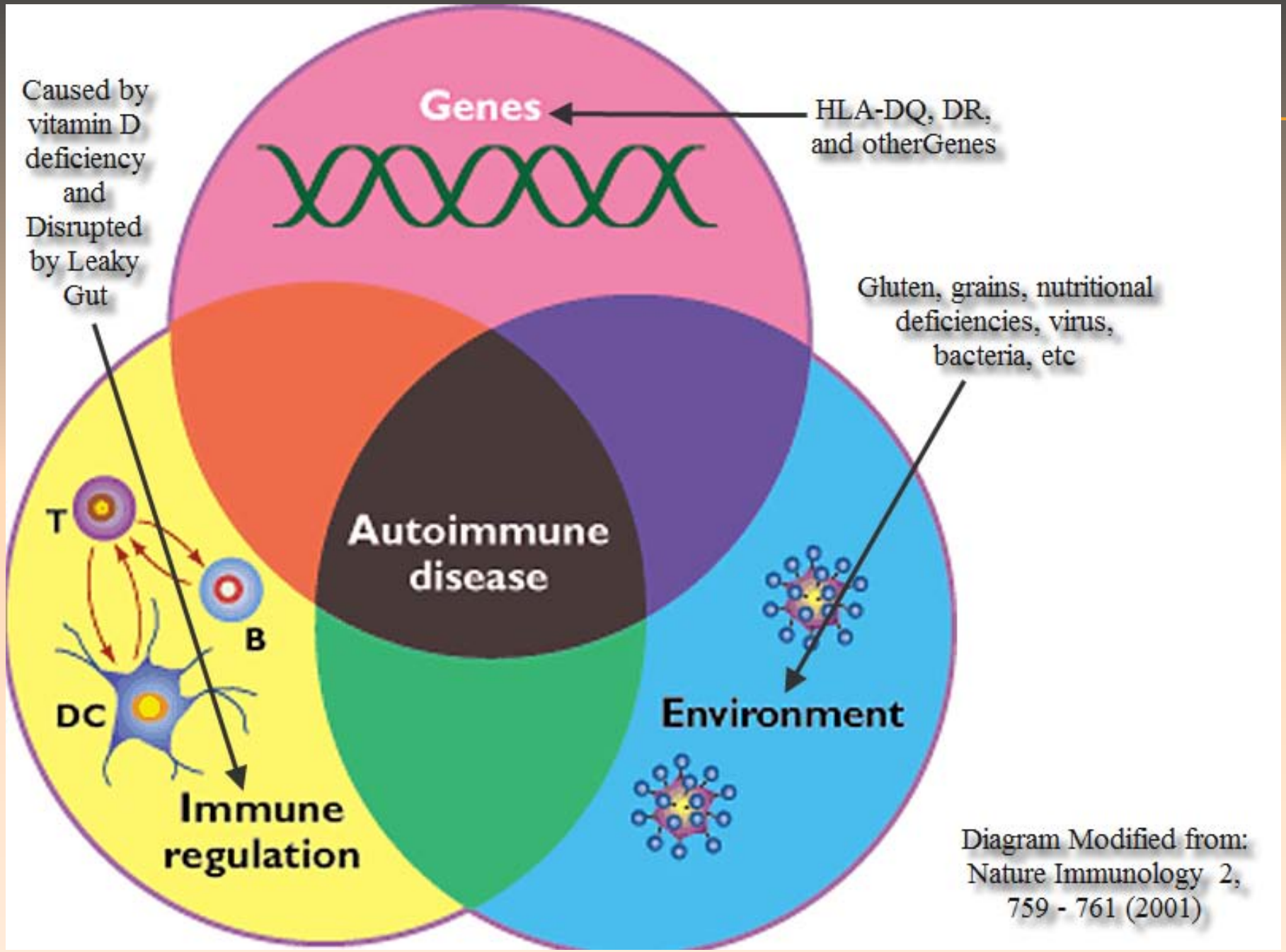
1.Genetic Factors

- Genetic studies have shown that autoimmune diseases are multigenic. This means that many genes contribute to susceptibility to the disease.

- This is different from diseases, such as cystic fibrosis, which are caused by mutations in a single gene.

- Many autoimmune diseases exhibit a marked familial incidence, which suggests a **genetic predisposition** to these disorders.

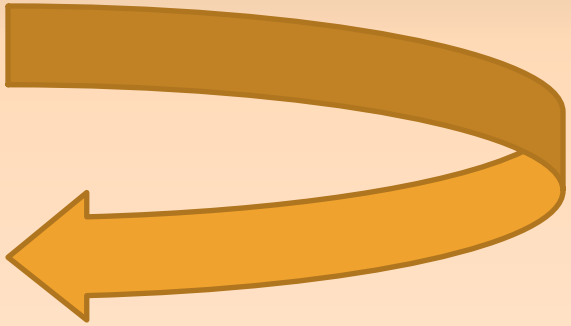
There is a strong association of some diseases with certain human leukocyte antigen (HLA) specificities, especially the class II genes.


Caused by vitamin D deficiency and Disrupted by Leaky Gut
Genes
HLA-DQ, DR, and otherGenes
Gluten, grains, nutritional deficiencies, virus, bacteria, etc
T
B
DC
Autoimmune disease
Environment
Immune regulation
Diagram Modified from: Nature Immunology 2, 759 - 761 (2001)

In general, class II MHC-related diseases, e.g.:

- Rheumatoid arthritis,
- Graves' disease (hyperthyroidism)
- systemic lupus erythematosus,

occur more commonly in women.



whereas class I MHC-related diseases:
Reiter's syndrome, occur more commonly in men.

2.Hormonal Factors

Approximately **90% of all autoimmune diseases occur in women.**

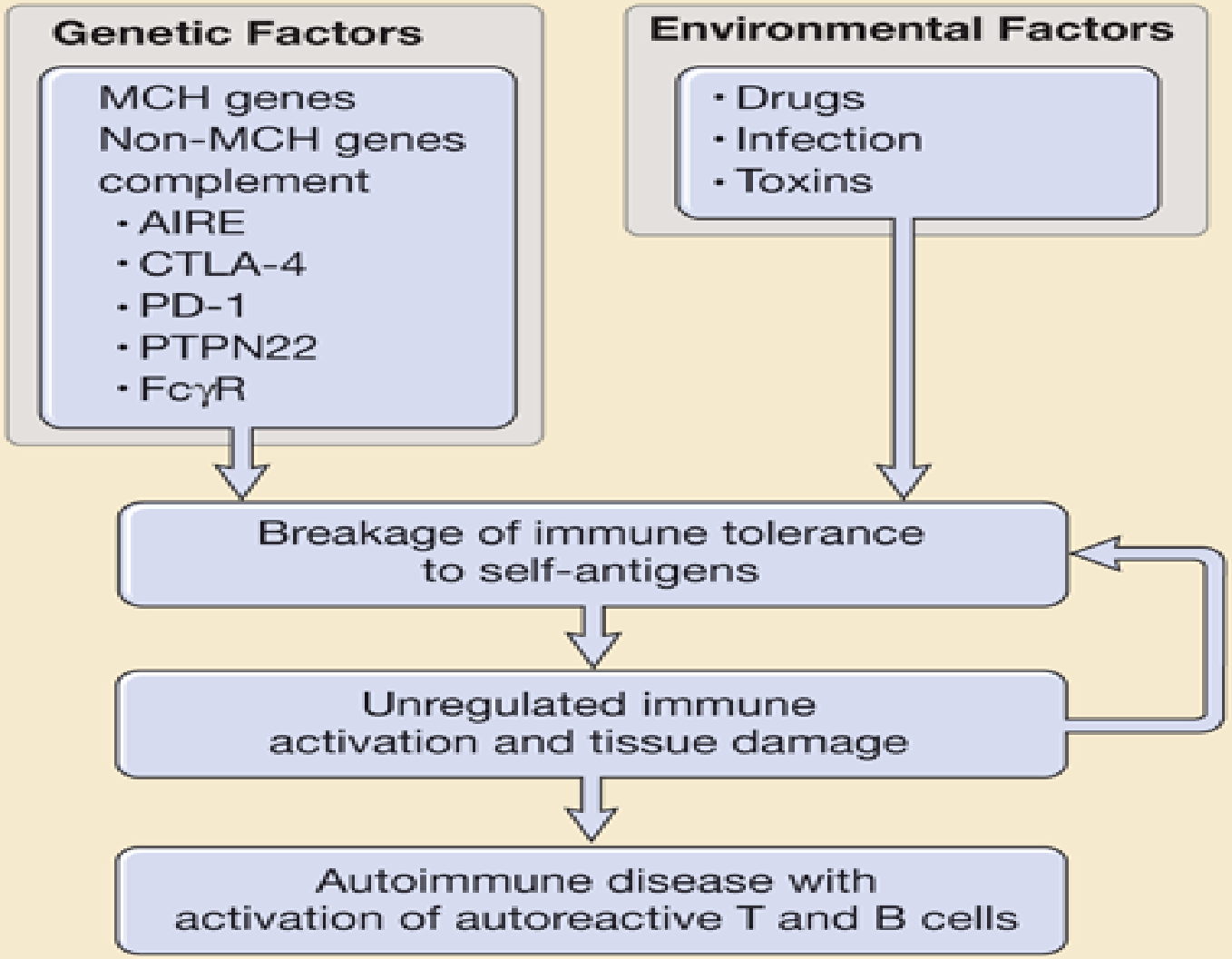
3.Environmental Factors

There are several environmental agents that trigger autoimmune diseases, most of which are either bacteria or viruses.

For example, pharyngitis caused by *Streptococcus pyogenes* predisposes to rheumatic fever.

THE MAIN TYPES OF ENVIRONMENTAL FACTOR ASSOCIATED WITH AUTOIMMUNITY INCLUDE THE FOLLOWING:

Mechanisms for autoimmune diseases



Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

•**Infectious agents.** The best-known example of infectious agents contributing to autoimmunity is rheumatic fever, where antibodies against streptococcal M-antigen react against heart myosin, joints and kidney, resulting in arthritis and heart disease

•**Drugs.** Drugs or their metabolites can bind to self-antigens and make them appear foreign. This can result in the development of autoantibody against the self-antigen itself Examples of this, are penicillin metabolites, which bind to red blood cells.

•**Toxins and pollutants**. In an autoimmune disease called Goodpasture's syndrome, autoantibodies are produced against type IV collagen, which is present in the basement membranes of the kidney and lung.

•**Food.**

PALEOHACKS

— THE 10 BEST — ANTI-INFLAMMATORY FOODS

COLD-WATER FATTY FISH

GRASS-FED & WILD GAME MEATS

TURMERIC ROOT

GINGER

LEAFY GREENS

HOT PEPPERS

BLUEBERRIES

BEETS

PINEAPPLE

BROCCOLI

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TOP 10

Foods that Prevent Inflammation in Your Body

Olive Oil

Ginger

Turmeric

Garlic

Tart Cherries

Salmon

Sweet Potatoes

Spinach

Walnuts

To explore more, visit

Top 10 Home Remedies

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Blueberries

THANK YOU