Tolerance And Autoimmune Diseases

Tolerance

Definition: The absence of specific immune responses to self antigens in a immunocompetent person

*** Both B-cells and T-cells participate in tolerance but tolerance in B cells is incomplete therefore most of the autoimmune diseases are due to autoantibodies**

- **But T-cells play the primary role**

How to control autoimmune diseases?

Answer: by maintaining the immunological tolerance to self antigens in both primary lymphoid organs and peripheral L.Os accordingly there Are two kinds of tolerance:
A) Central tolerance. B) Peripheral tolerance

Mechanism of tolerance
A- Autotolerance (Central and peripheral tolerance)
B- Acquired tolerance

Central Tolerance

T-cells which express high affinity receptors for self antigens are deleted by a physiological process called apoptosis (programmed cell death), this process usually occur in medulla of thymus and called negative selection. Immature T cells that recognize and bind with MHC molecules are selected to be mature (positive selection) which occurs in the cortex of the thymus, while immature T cells that ignore self antigen with MHC molecules are killed by apoptosis.

Peripheral Tolerance

Some T-cells which express receptors for self antigens but not encounter Self antigens in the thymus and released into the peripheral lymphoid Organs such as Lymph nodes where they undergo tolerance by Different mechanisms:

1- Clonal deletion by induced cell death (apoptosis)
2- Inhibition (Clonal anergy)
3- Suppression by regulatory T-cells
4- Immune privilege
5-Immunosuppression cytokines like IL-10 and TGF-beta

1- Inhibition (clonal anergy)

Mechanisms

1-During presentation of self Ag via APCs to TH cells will not be activated by

A- No making CD40 L so TH cell will not be activated and this called inhibition or clonal anergy.

B- CTLA-4 (cytotoxic T lymphocytes associated protein 4) from TH cells will bind with B-7 (inhibition)

2- Clonal deletion

Mechanisms

TH cells will express Fas and FasL

3- Immunological privilege or ignorance

Sequestered Ag (sperm, eye lenses protein) these self proteins never exposed to T and B cells during maturation so when enter blood circulation , immune cells can not recognize them (immunological ignorance).

4- Suppression

By T reg cells which express CTLA-4 and TGF that suppress immunity.

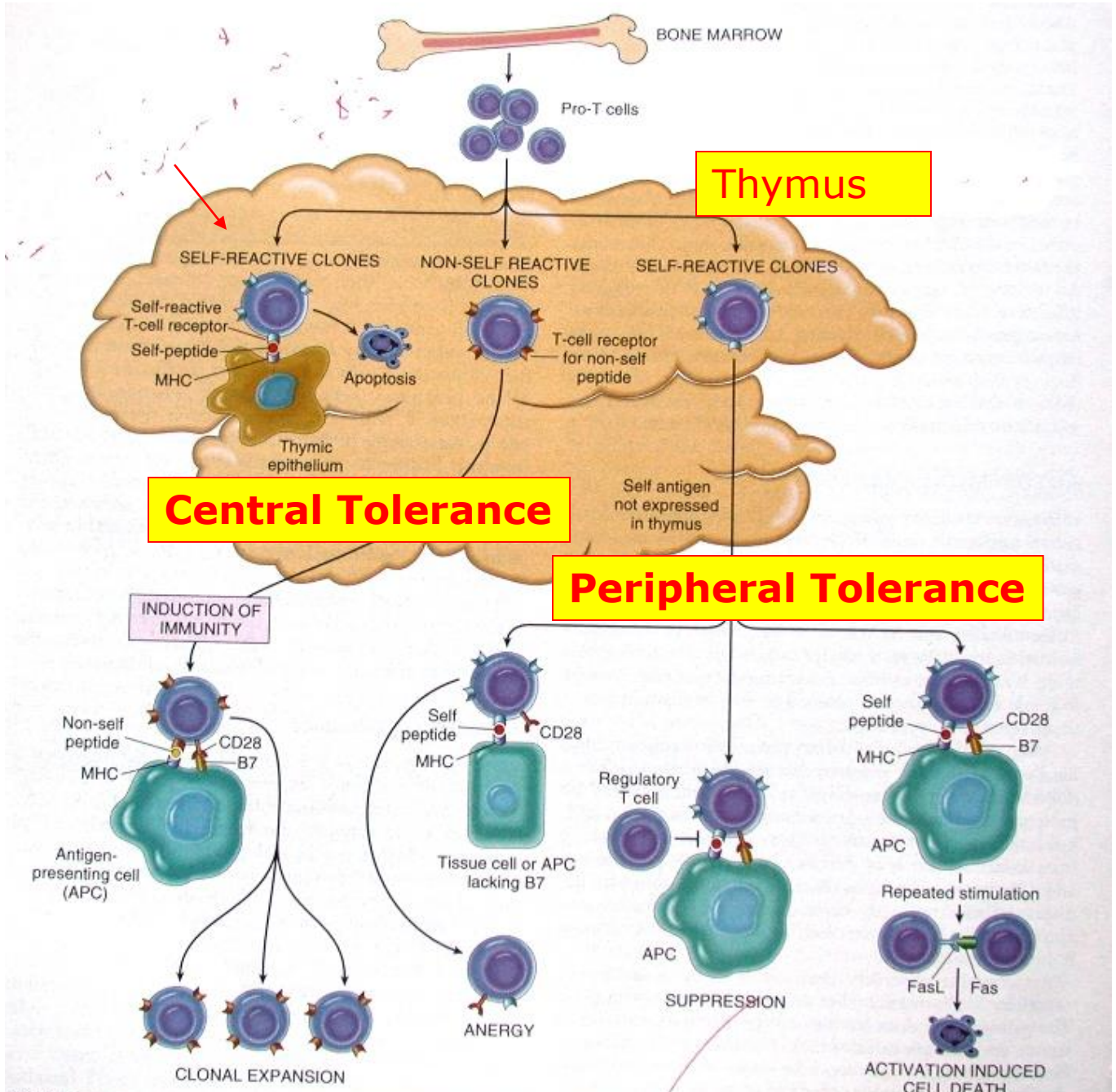


FIGURE 6–27 Schematic illustration of the mechanisms involved in central and peripheral tolerance. The principal mechanisms of tolerance in CD4+ T cells are shown. APC, antigen-presenting cell

Acquired tolerance (induced)

Definition: Induction of tolerance to an Ag at any time during life which used for treatment of:

A- Allergic conditions

B- Graft rejection

C- Autoimmune diseases

How to make antigen toleragen?

1- Giving high or low dose of Ag----toleragen

2- Converting protein Ag into soluble Ag

3- Rpeated administration of Ag----toleragen

4- Give an Ag with immunosuppressive drugs

5- Toleragenic is easier neonates

Autoimmune diseases

Definition: Immune response to self Ag (Break down of tolerance)

Causes of development of autoimmune diseases

1- T cells released into peripheral without education.
2- Releasing of sequestrating Ag like damage of testes or eye lens.
3- Molecular mimicry like Post Streptococcal Rheumatic fever.
4- Polyclonal antibodies Like EB virus induce polyclonal antibodies and some of these Abs cross react with self antigens.
5- Increased TH17 cells function (IL-17 promote cellular immunity but overproduction of IL-17 is associated with many autoimmune diseases like RA, SLE, MS and asthma).
6- Defect in Fas and FasL that leads to T cell activation
7- Altered autoantigens (like drug induced autoimmune hemolytic anemia)
8- Genetic predisposition

- HLA-B27 with ankylosing spondylitis
- HLA-DR2 with MS
- HLA-B8 with myasthenia gravis
- HLA-DR4 with RA
- HLA-DR5 with hashimotos thyroididtis

9- Estrogen

- ❑ Enhance B cell activity
- ❑ Suppress the regulation of T cells

Classification of autoimmune diseases

Organ specific

1- Hashimotos disease
2- Graves disease
3- Myasthenia gravis
4- Pernicious anemia
5- Addisons disease
6- Insulin DM
7- Autoimmune hemolytic anemia
8-Celiac disease

Non organ specific

1- SLE
2-RA
3-MA

1- Hashimotos disease (Chronic lymphocytic thyroiditis)

Mechanisms: The immune system attacks thyroid gland cells (Hypothyroidism= TSH is high while both T3 and T4 are low

Lab.diagnosis

1- Thyroid function test (TSH is high while T3 and T4 are low)

2- Anti-thyroperoxidase Ab (Anti-TPO is high)

3- Anti-thyroblobulin Ab (is high) (both above enzymes and thyroglobulin are important for synthesis of T3 and T4) (specific tests)

2- Graves disease

Mechanisms: Autoantobodies against TSH receptors (overstimulation) (hyperthyroidism or thyrotoxicosis= type II HSR cytolytic activated)

Lab.diagnosis

1- Thyroid function test (TSH is loo while T3 and T4 are high)

3- Myasthenia gravis

Mechanisms: Autoantibodies against ACH receptors so no muscle contraction (Type II HSR Non cytolytic (blocking) **.**

Lab.diagnosis

1-Anti ACHR Ab. (dropping of eye lids, difficulty in swallowing and chewing problem)

4- Pernicious anemia

Mechanisms: Autoantibodies against intrinsic factor so Vit.B12 absorption (macrocytic anemia)

Lab.diagnosis

1- CBC (low Hb level)

2- Anti IF Ab test

4- Immune hepatitis

Check for the following autoantibodies

1- Anti nuclear antibodies (ANA)

2- Anti-mitochondrial Ab (AMA) more specific

3- Anti smooth muscle Ab (ASMA) more specific

5- SLE

Definition: It a connective tissue systemic autoimmune disease that attack

- Skin
- Joints
- Kidneys
- Heart
- Lungs More in females than males

Mechanism: Autoantibodies against cell components (histone. Ds-DNA. Platelets)---- formation of soluble Ics that if deposited in skin (butter fly face), in Kidney (dysfunction), in heart (myocarditis or endocarditis)

Lab.Diagnosis of SLE

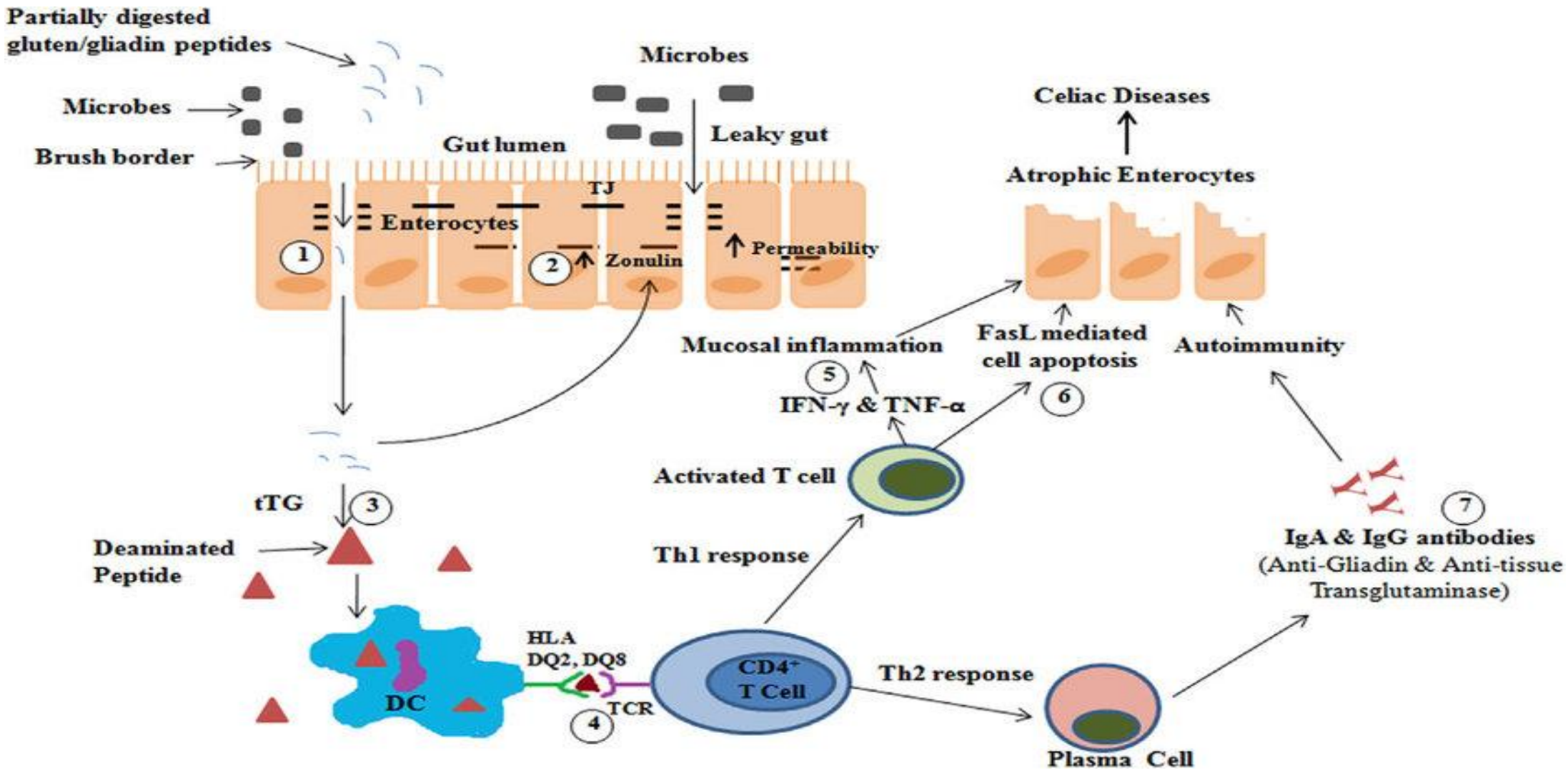
1- CBC (anemia)
2- ESR (high)
3- RFT (abnormal)
4- ANA (non specific)
5- Anti ds-DNA (more specific)
6- Anti sm Ab (more specific)

Rheumatoid arthristis

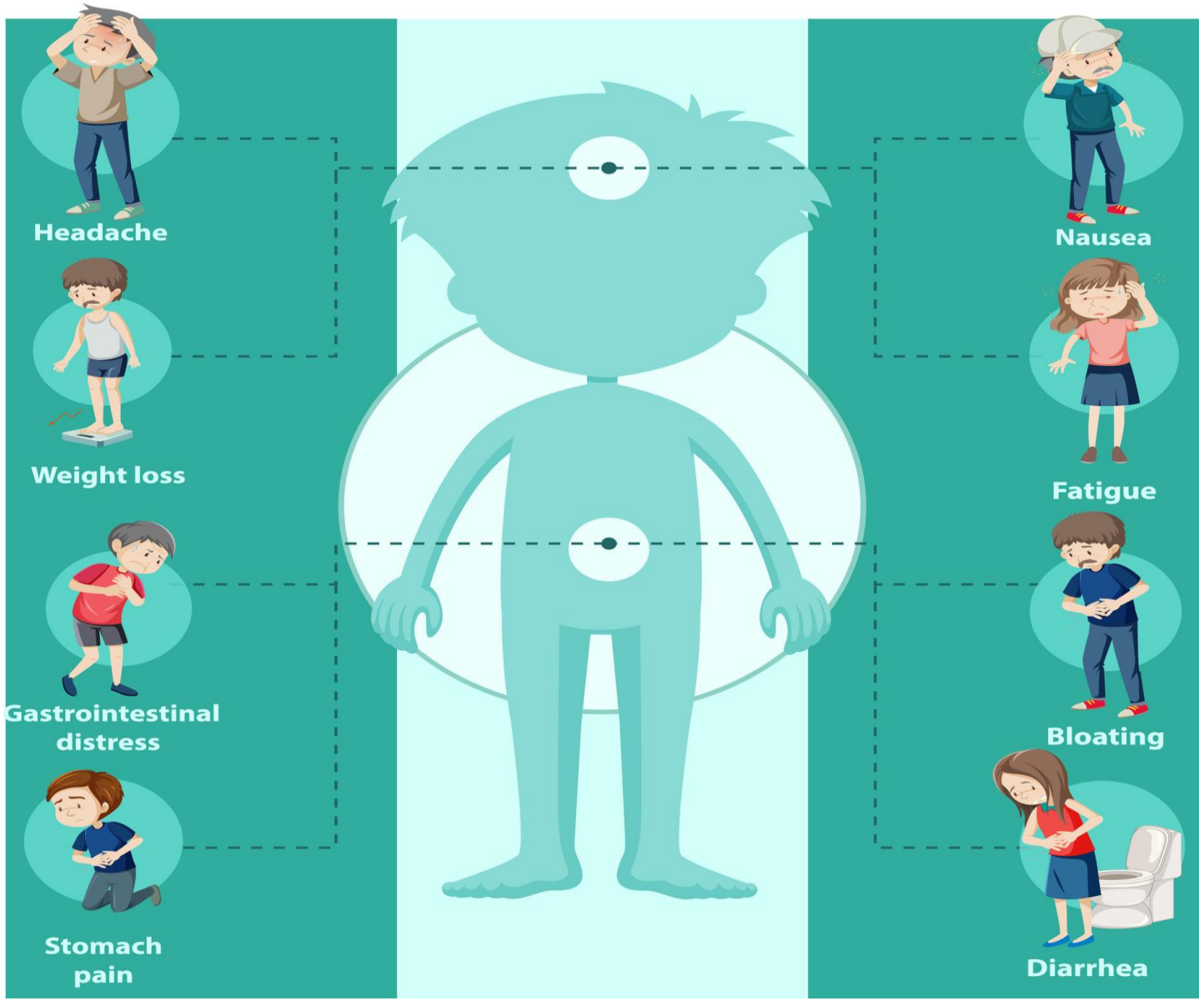
Definition: Autoantibodies against synovial membrane of the joints

Mechanisms: Fc of IgG act as foreign making IgM –IC-deposited in synovial membrane (type II HSR)
Arginine change to Citrulline which make Anti-cyclic citrulline peptide Ab **(Anti-CCP Ab)** specific diagnostic test.

Pathogenesis of celiac disease



CELIAC DISEASE – SYMPTOMS



Lab.Diagnosis of Celiac disease

1- Duodenal biopsy (gold standard) –villus atrophy

2- Serology (celiac disease profile (Anti-gliadin IgA, IgG; Anti tissue transglutamase = anti-tTG –IgA and IgG

TABLE 16-1 Some autoimmune diseases in humans

Disease	Self antigen	Immune response
	ORGAN-SPECIFIC AUTOIMMUNE DISEASES	
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_H1 cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_H1 cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
	SYSTEMIC AUTOIMMUNE DISEASES	
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_H1 cells and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjögren's syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes

Table 16-1
Kuby IMMUNOLOGY, Sixth Edition

Do you know?

- We want immune tolerance in case of organ transplantation to not be rejected.
- We do not want to be tolerance for tumors but unfortunately we are tolerant for them and finally they kill us without mercy.

Thanks