Autoimmune diseases and tolerance

Dr.Eman Albataineh,
Prof. Immunology
College of Medicine, Mu'tah university
Immunology, 2nd year students

Tolerance

- Immunologic tolerance is defined as unresponsiveness to an antigen
- Antigens that induce tolerance are called tolerogens, or tolerogenic antigens, to distinguish them from immunogens, which generate immunity
- and failure of self-tolerance results in immune reactions against self (autologous) antigens. Such reactions are called autoimmunity

- Main contributor to tolerance is CD4 T cells because
  - MHC relation to autoimmune diseases
  - T cell is the key regulator of immune response to proteins
- Tolerance in CD4+ helper T lymphocytes is an effective way of preventing both cell-mediated and humoral immune responses to auto protein antigens because helper T cells are necessary inducers of all such responses
- Ways of tolerance
  - Central tolerance; selection, T reg
  - Peripheral tolerance= T cells regulation

- Mechanisms of **central** self tolerance
  - In T cell selection stage; Medullary thymic epithelial cells can express self antigens that related to many organs and this controlled by many genes one is called Aire (autoimmune regulatory) (Aire deficient cause polyendocrinopathy syndrome, addison, hypoparathyroid and chronic candidiasis.) if they react to the self antigen they die or differentiated to T reg.

❖ Peripheral tolerance

- Auto-reactive T cells may result because fail of T cell regulation,
  - Fail of expression of CTLA-4 after T cell activation
  - Fail of activation induced cell death by death receptors (Fas-FasL) on NK or Tc in the case of persistent T cell activation,
  - Fail of Activation of PD-1 and PD-1L binding
- or because presence of co-stimulatory signals (B7) on APC in chronic infection the absence of antigen

B lymphocytes tolerance

- Central
  - Editing, deletion and anergy
- Peripheral
  - absence of specific helper T cells, B cells may be rendered functionally unresponsive or die by apoptosis
  - Expression of death protiens; Fas on B cell and Fas L on Tc or NK, inhibitory receptor CD22 and inhibitory Fc receptor (FcγRIIB).
- polymorphism of this inhibitory Fc receptor (FcγRIIB). impairs inhibitory signaling and is associated with SLE in humans

Uses of induction of tolerance

- Tolerance induction may also be useful for
  - preventing immune reactions to the products of newly expressed genes in gene therapy protocols,
  - for preventing reactions to injected proteins in patients with deficiencies of these proteins (e.g., hemophiliacs treated with factor VIII),
  - for promoting acceptance of stem cell transplants, and graft transplantation
  - In autoimmune diseases
  - and in immunotherapy for allergy to foreign proteins.

Ways of induction tolerance

- In general, protein antigens administered cutaneously with adjuvants favor immunity, whereas antigens administered without adjuvants tend to induce tolerance.
- Immunosuppression by total body irradiation, drugs (cyclosporin and anti-lymphocytic antibodies as anti-CD4, soluble CTLA-4, steroids
- Oral administration of antigens for long time

Autoimmune diseases, etiology

- Multifactorial and some unknown
- Environmental as nutrition, radiation and drugs
- After infection, trauma or surgery
- Release of sequestrated antigens as a result of tissue injury.g; Post-trauma, exposed antigens of nucleus in SLE (systemic lupus erythromatosus) that immune system did not expose to before. epitope spreading,
- Exposure to microbial antigens that cross react(means immune reaction against antigen other than antigen that presented first) with self antigens (molecular mimicry); strep-pyogenes and rheumatic fever. It has also been found that similarities in structure between certain bacterial protein fragments and fragments of gluten proteins may be key in contributing to gluten disorders, including Celiac disease.

Follow etiology

- Chronic Inflammation may also lead to enhanced expression of costimulators in surrounding tissues and by pro-inflammatory mediators. Thus, the infection results in the activation of T cells in the absence of antigen (bystander activation) as in CD8 activation in T1DM and MS.

- Genetic pre-disposition (Polygenic); Rheumatoid arthritis (RA)in HLADR4, thyroiditis in HLA DR5, multiple sclerosis in HLA DR2, systemic lupus erythromatosus (SLE) in HLA DR3, Type 1 diabetes in HLA DR3 and 4

celiac disease HLA-DQ 2 or HLA-DQ 8

- Other genetics (single gene), loss of fas, fasL expression or CTLA-4 gene mutations(lymphoproliferative) . AIRE gene (polyendocrine syndrome), C4 gene (SLE)
- Hormonal factors, RA and SLE more in females

Examples Of Single-gene Mutations That Cause Autoimmune Disease

Gene	Phenotype of Mutant of Knockout Mouse	Mechanism of Failure of Tolerance	Human Disease?
AIRE	Destruction of endocrine organs by antibodies, lymphocytes	Failure of central tolerance	Autoimmune polyendocrine syndrome (APS)
C4	SLE	Defective clearance of immune complexes; failure of B cell tolerance?	SLE
CTLA-4	Lymphoproliferation; T cell infiltrates in multiple organs, especially heart; lethal by 3-4 weeks	Failure of anergy in CD4+ T cells; defective function of regulatory T cells	CTLA-4 polymorphisms associated with several autoimmune diseases
Fas/FasL	Anti-DNA and other autoantibodies; immune complex nephritis; arthritis; lymphoproliferation	Defective deletion of anergic self-reactive B cells; reduced deletion of mature CD4+ T cells	Autoimmune lymphoproliferative syndrome (ALPS)
FoxP3	Multiorgan lymphocytic infiltrates, wasting	Deficiency of functional regulatory T cells	IPEX
IL-2, IL-2Rα/β	Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies	Defective development, survival, or function of regulatory T cells	None known
SHP-1	Multiple autoantibodies	Failure of negative regulation of B cells	None known

AIRE, autoimmune regulator gene; *IL-2*, interleukin-2; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; *SHP-1*, SH2-containing phosphatase 1; SLE, systemic lupus erythematosus

Classification of autoimmune

- **Organ-specific disorders** (also called *localized*) focus on one organ or a specific type of tissue. Among those that can affect children are:
- Addison's disease (adrenal glands) outer portion of your adrenal glands (the adrenal cortex), where they make cortisol and aldosterone
- celiac disease (gastrointestinal tract), transglutaminase
- Inflammatory bowel disease Ulcerative colitis primarily targets the mucosa of the colon in a continuous pattern, whereas Crohn's disease can affect any part of the GI tract and it is penetrating
- multiple sclerosis (MS)(brain/spinal cord)
- type 1 diabetes (pancreas ilets Beta cells)
- Gravis and Hashimoto thyroiditis

- **Non-organ-specific disorders** (also called *systemic*) cause problems more widely throughout the body. Among those that can affect children are:
- **Rheumatic fever** (joints ,skin and heart)
- **lupus (SLE)** (joints, skin, kidneys, heart, brain and others)
- **Rheumatoid arthritis (RA) (joints, skin, muscles)**
- **Psoriasis** is over growth of the skin epidermal layer, Th17 and TH1 cell attack (type 4) the skin epidermis and joint. (cluster plaques on the skin)

The spectrum of autoimmune disease

Organ Specific Autoimmune Diseases

Graves Disease	(Thyroid: TSHR Abs, TPO Abs)
Hashimoto Thytreoiditis	(Thyroid: TPO Abs, Tg Abs)
Diabetes Type I	(Pankreas: GAD II Abs, IA2 Abs, ICA)
Goodpasture Syndrome	(Kidney: GBM Abs)
Pernicious Anemia	(Stomach: Parietal Cell Abs)
Primary Biliary Cirrhosis	(Liver, Bile: AMAbs)
Myasthenia Gravis	(Muscles: AChR Abs)
Dermato-/Polymyositis	(Skin / Muscles: Jo 1 Abs)
Vasculitis	(Vessels: ANCA)
Rheumatoid Arthritis	(Joints: CRP, RF, RA33 Abs, Sa Abs)
MCTD	(RNP Abs)
Scleroderma	(Scl 70 Abs, CENP Abs, PM/Scl Abs)
SLE	(ANA, Cardiolipin Abs, Beta 2 GP I Abs)

Multi-systemic Autoimmune Diseases

- Mechanisms of tissue damage (hypersensitivity reactions)
  - Bound self antigens (type 2 hypersensitivity) as autoimmune hemolytic anemia, myasthenia gravis, Hashimoto thyroiditis, good Pasteur and rheumatic fever
  - Immune complex deposition; type 3 as SLE and RA
  - Cell mediate (Type 4), as Multiple sclerosis (MS), RA, type 1 diabetes, psoriasis and ulcerative colitis
- Once autoimmune disease start it become chronic and progressive due to epitope spreading as a result of tissue damage
- The symptoms is on and off, when it is on it is called flare up.

Some common autoimmune diseases classified by immunopathogenic mechanism		
Syndrome	**Autoantigen**	**Consequence**
Type II antibody to cell-surface or matrix antigens		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and FcR^+ phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin GpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Noncollagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Type III immune-complex disease		
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, rash
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis
Type IV T cell-mediated disease		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-Cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, weakness

Lab. diagnosis

- Elevated levels of immunoglobulins
- High CRP, ESR
- Auto-antibodies; anti-nuclear (ANA) systemic lupus erythematosus, Sjogren's syndrome, scleroderma or mixed connective tissue disease.RA
- rheumatoid factor (RF) in RA
- Complement levels may decreased
- Biopsy and immunofluorescent microscope; Antibody on the surface of the tissue or cells, immune complex or lymphocyte infiltration

Management

- Anti-inflammatory drugs; aspirin, corticosteroids
- Immuno-suppressive drugs, azathioprine
- plasmapheresis

Myasthenia gravis

- MG is Ab against acetylcholine receptor of neuromuscular junction, block receptor and cause muscle weakness
- **Gravis disease**
  - Antibodies against thyroid stimulating hormone receptor cause long lasting activation and hyperthyroidism
- **Idiopathic thrombocytic purpura (platelet antigen) low platelet count+bleeding**
- **Good pasteur syndrome (renal and lung basement membrane collagen)lung and kidney bleeding; anti-glomerular basement membrane (GBM)**
- **Vitiligo (melanocytes) lead to depigmentation of skin**

Multiple sclerosis

- Antibodies against myelin basic protein (MBP) (Type 2 hypersensitivity)
- Also cell infiltration with TH1 and TH17 and cytokine as TNF alpha (type 4)
- Demyelination, perivascular inflammation, paralysis and ocular lesions
- No certain treatment, disease modifying agents as interferon beta, anti-CD20 to deplete B cells, injection of MBP to induce tolerance

Hashimoto thyroiditis

- Antibodies against thyroglobulin and/or thyro-pyroxidase (TPO) antigens (type 2 hypersensitivity)
- hypothyroidism, and hard and large gland due to lymphocytic infiltrate (type 4 hypersensitivity)
- Treatment, thyroid hormone replacement

Autoimmune Disease	II	III	IV
Diabetes Mellitus (Type I)	x		x
Acute Transplant Rejection	x		x
Pernicious Anemia	x		x
Hashimoto's Thyroiditis	x		x
SLE (lupus)	x	x	
Rheumatoid Arthritis		x	x
Hypersensitivity Pneumonitis		x	x

Type 1 diabetes

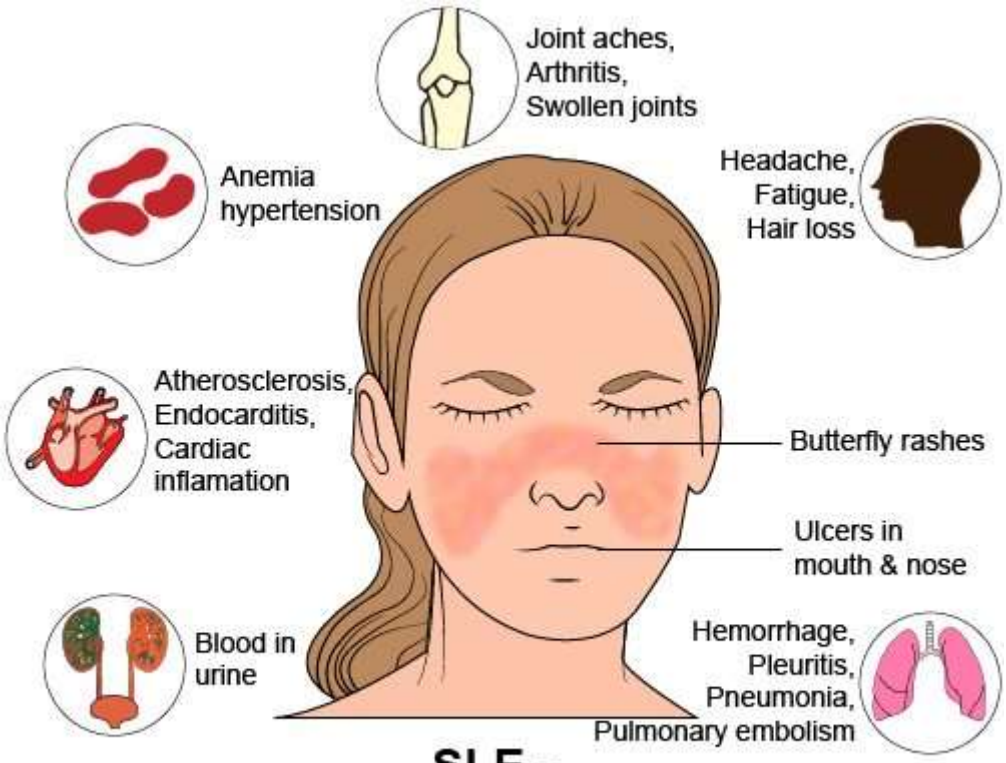
- Antibodies against pancreatic beta cell protein (insulin) (type 2) glutamic acid decarboxylase (GAD) antibody is a biomarker
- Or infiltration with cells TH1 and CD8 and (type 4)
- cytokine effect (IL-1 and TNF alpha)
- Lead to beta cell destruction and absence of insulin
- Can be differentiated from type 2 DM by autoantibody testing
- Symptoms polydepsia, polyphagis, polyuria
- Treatment, insulin therapy, immune therapy by induce tolerance to diabetic antigen.

Inflammatory bowel disease consists of two disorders, Crohn's disease and ulcerative colitis, in which T cell–mediated inflammation causes intestinal injury. Crohn's disease is characterized by chronic inflammation and destruction of the intestinal wall, with frequent formation of fistulas. In ulcerative colitis, the lesions are largely confined to the mucosa and consist of ulcers

Causes of inflammatory bowel disease are mainly genetic and cellular infiltration mainly TH1 and TH17 (type 4)

SLE (Systemic lupus erythematosus)

- Red flush on face as wings of butterfly, disease attack many organs as CNS, heart and kidney
- Mechanisms; 95% of patients have Abs to DNA and RNA (anti-nuclear Ab (ANA), and more specific anti-ds-DNA antibody
- Circulating immune complexes deposit in skin (vasculitis, skin rash), basement membrane of kidney (lampy bumpy deposits) lead to glumerolonephritis and proteinuria
- Mechanism of destruction (type2 and 3 hypersensitivity)
- as a result of tissue damage, exposed DNA attacked by Ab)



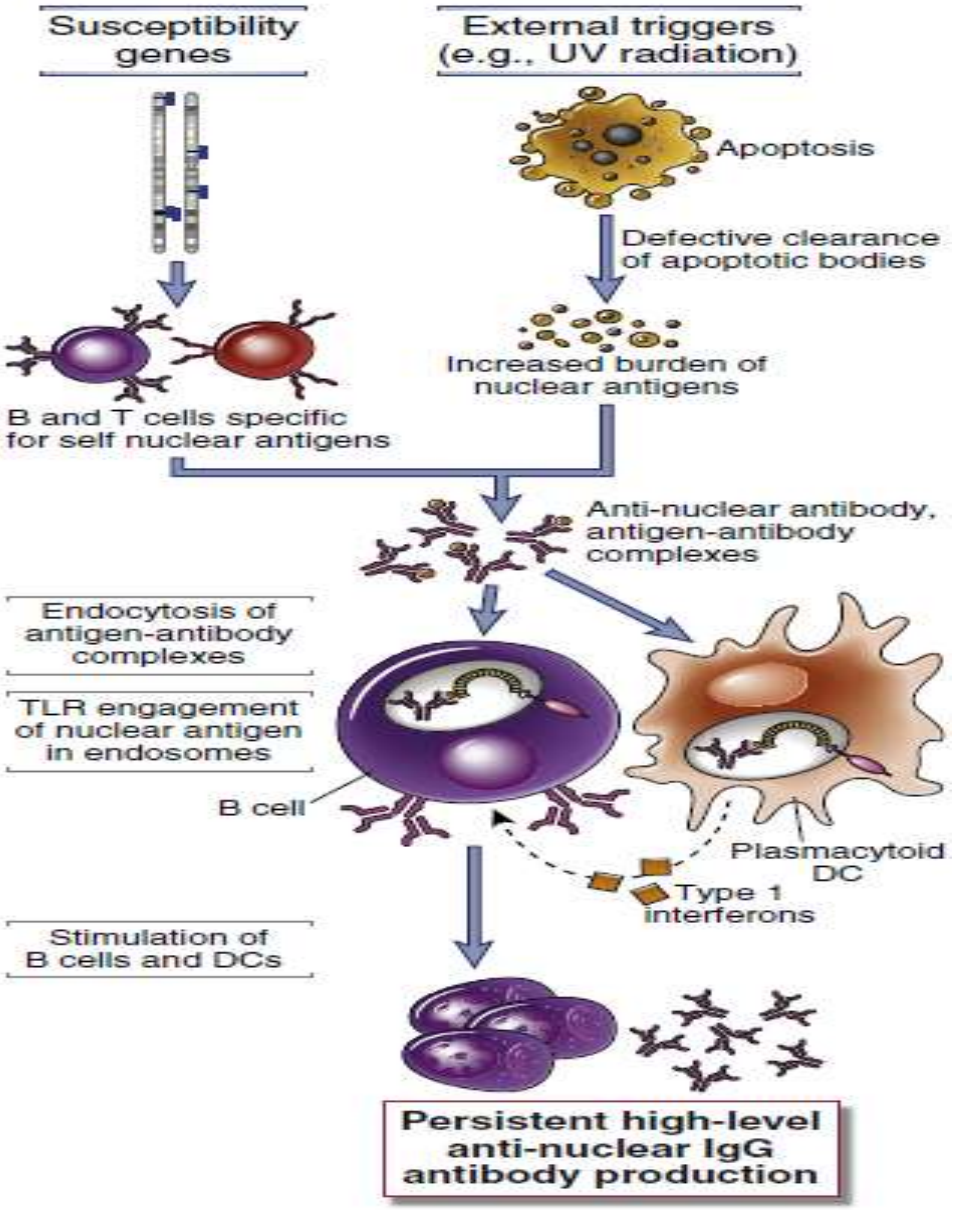
SLE -
Systemic LUPUS Erythmatosus

FACTDr

SLE

- Diagnosis,
  - Symptoms as skin rash, proteinuria and edema
  - Tissue biobsy; immunoflourescence microscope (granular appearance or linear)) to see ANA or immune complexes,
  - Blood levels of ANA and anti-DS DNA antibody
  - low complement levels
  - Treatment
    - Corticosteroids, pain killers, methotrexate
    - (anti-folate that inhibit synthesis of DNA, and RNA) so prevent or stop immune cells growth
    - anti-inflammatory drug sulfasalazine

SLE

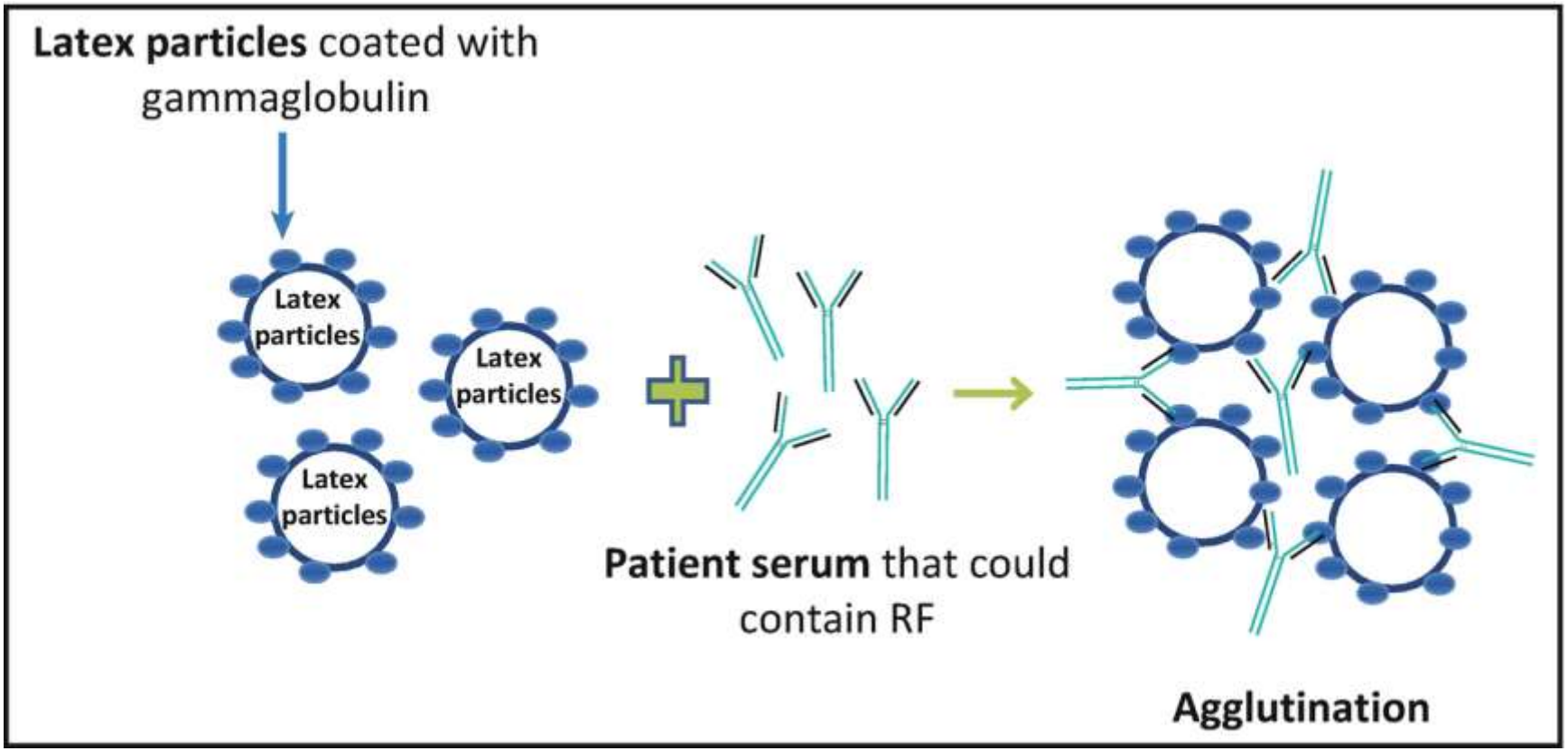

Susceptibility genes
External triggers (e.g., UV radiation)
Apoptosis
Defective clearance of apoptotic bodies
Increased burden of nuclear antigens
B and T cells specific for self nuclear antigens
Anti-nuclear antibody, antigen-antibody complexes
Endocytosis of antigen-antibody complexes
TLR engagement of nuclear antigen in endosomes
B cell
Plasmacytoid DC
Type 1 interferons
Stimulation of B cells and DCs
Persistent high-level anti-nuclear IgG antibody production

New Therapies for Systemic Lupus Erythematosus

The recent advances in our understanding of SLE are leading to novel therapeutic approaches. Clinical trials are under way to test the efficacy of anti–IFN-α antibodies in the disease, and attempts to inhibit TLR signals are being considered. There has been great interest in depleting B cells by use of an antibody against the B cell surface protein CD20. An antibody that blocks the B cell growth factor BAFF is now approved for the treatment of SLE.

Rheumatoid arthritis

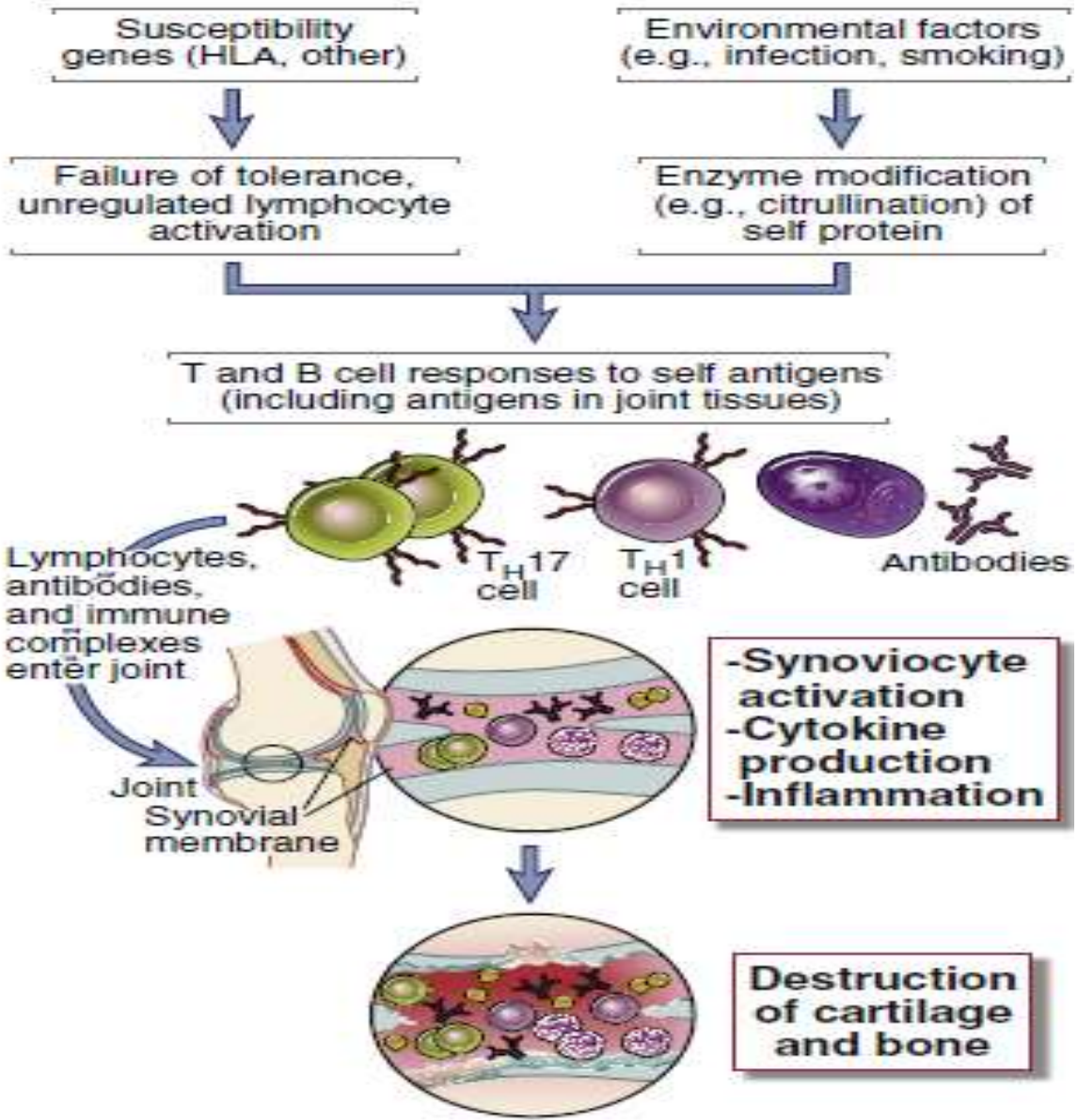
- Synovium full with lymphocytes and immune complexes leading to destruction of bone and cartilage
- Causes
  - rheumatic factor (RF): Auto-antibodies mainly IGM but may be IGG, against Fc portion of self IGG and this factor present in 90% of patients
  - Tissue damage by Type 3 hypersensitivity reaction (Immune complexes), by anti-CCP antibody or RF and antigen complexes
  - Or Type 4 reaction; TH1, CD8 cells, IL-1, IL-6 and TNF alpha cytokines against antigens in synovial membrane of the joint
  - anti-nuclear Abs (ANA) in 50% of patients
  - Stiff painful joints, malformation in Joint x-ray
  - Diagnostic test, positive RF latex agglutination test. mixes the patient's serum with tiny latex beads covered with human antibodies (IgG). The latex beads clump or agglutinate if rheumatoid factor is present in patient serum.


Latex particles coated with gammaglobulin
Latex particles
Latex particles
Latex particles
Patient serum that could contain RF
Agglutination

Anti-CCP

- During inflammation, amino acid change in the patient normal protein, by a process called citrullination. That lead to generation of new antigenic epitopes
- Anti-citrullinated protein antibodies (ACPAs) are formed. They are present in the majority of patients with rheumatoid arthritis (70%) and they are frequently used for diagnosis in very early stages.

RA


Susceptibility genes (HLA, other)
Environmental factors (e.g., infection, smoking)
Failure of tolerance, unregulated lymphocyte activation
Enzyme modification (e.g., citrullination) of self protein
T and B cell responses to self antigens (including antigens in joint tissues)
Lymphocytes, antibodies, and immune complexes enter joint
T_H17 cell
T_H1 cell
Antibodies
Joint
Synovial membrane
-Synoviocyte activation
-Cytokine production
-Inflammation
Destruction of cartilage and bone

RA disease modifying agents

- Corticosteroids, pain killers, methotrexate

(anti-folate that inhibit synthesis of DNA, and RNA) so prevent or stop immune cells growth

- anti-inflammatory drug sulfasalazine

RA treatment

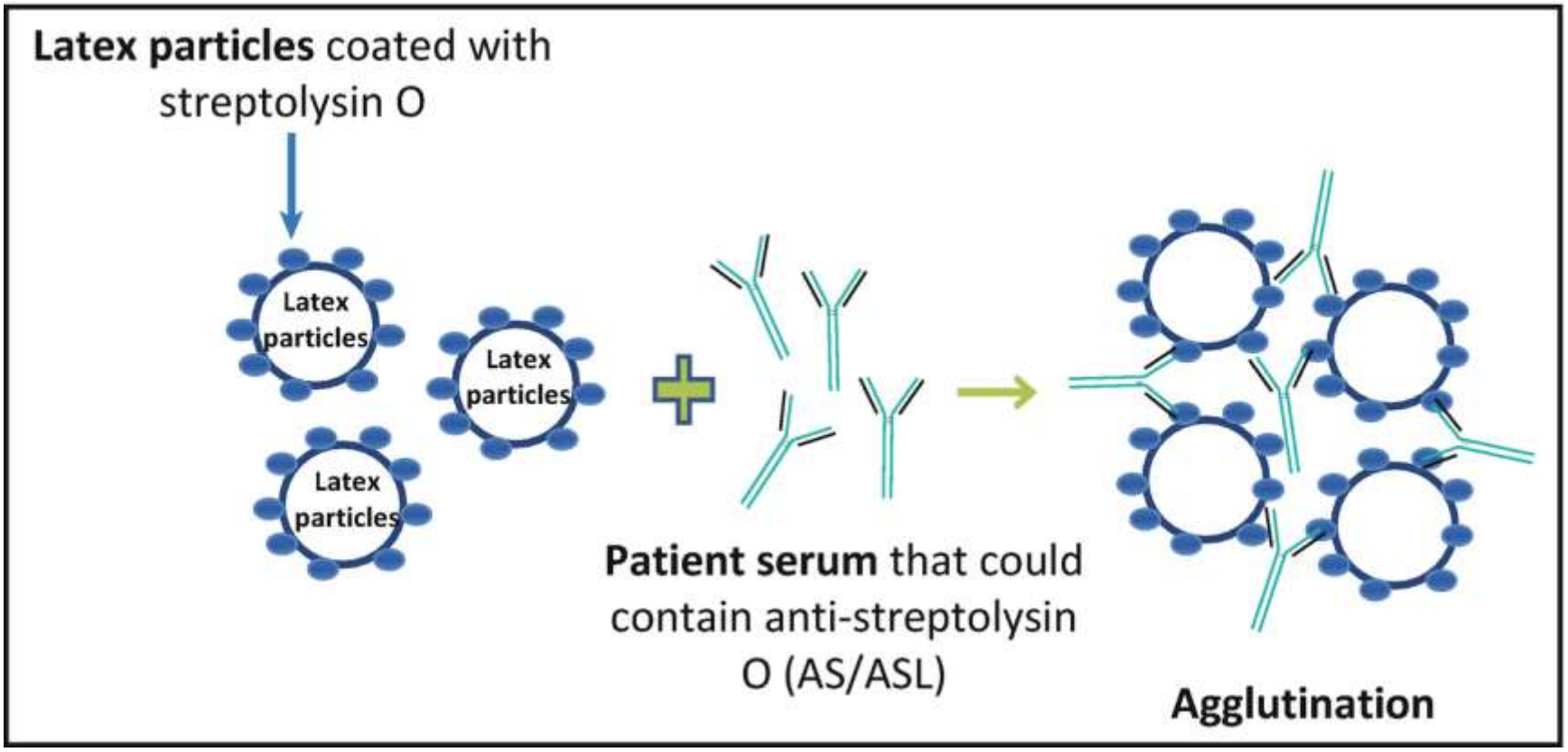
new therapies are antagonists against TNF, which have transformed the course of the disease in many patients from one of progressive and inexorable joint destruction to one of smoldering but manageable chronic inflammation. A variety of other targeted therapies have been developed in the past 5 to 10 years; these have provided insight into disease pathogenesis. Blockade of cytokines other than TNF has been effective, including an antibody the blocks the IL-6 receptor, an IL-1 antagonist, and a small molecule that inhibits JAK signaling (an important intracellular signaling mediator of a variety of cytokine receptors). Inhibition of T cell activation has been accomplished by blockade of B7:CD28 costimulation with CTLA-4-Ig, a fusion protein made of the extracellular domain of CTLA-4 and the Fc portion of IgG that binds B7 (see Chapter 9). B cell depletion with anti-CD20 antibody has also proven to be efficacious, although the mechanisms underlying this effect are not well understood.

Rheumatic fever

- **Rheumatic fever** is an inflammatory disease that occurs following a *Streptococcus pyogenes* infection, such as strep throat or scarlet fever. Believed to be caused by antibody cross-reactivity (Type 2 destruction) that can involve the heart, joints, skin, and brain the illness typically develops two to three weeks after a streptococcal infection. Acute rheumatic fever commonly appears in children between the ages of 6 and 15, with only 20% of first-time attacks occurring in adults. The illness is so named because of its similarity in presentation to rheumatism.

Diagnosis

- Elevated anti-ASO titer or **Anti-streptolysin O** (ASO or ASLO) is the antibody produced against an antigen produced by group A streptococci. The antigen is called *streptolysin O*, the titer varies being maximum 3-5 weeks after infection. the presence of Ab indicate exposure to these bacteria. diagnosis depend also on clinical presentation as some people have this antibody but normal.
- positive ASO latex agglutination test.


Latex particles coated with streptolysin O
Latex particles
Latex particles
Latex particles
Patient serum that could contain anti-streptolysin O (AS/ASL)
Agglutination

Connective tissue diseases

- Besides RA and SLE
- ANA present
- Scleroderma – an activation of immune cells that produces scar tissue in the skin, internal organs, and small blood vessels. Lead to tight skin appear in fingers and chest
- Sjögren's syndrome – also called Sjögren's disease, is a chronic, slowly progressing inability to secrete saliva and tears.
- Mixed connective tissue disease – (MCTD) is a disorder in anti-U1-ribonucleoprotein, Raynaud phenomenon, and features of at least 2 connective tissue diseases, including systemic lupus erythematosus, systemic sclerosis, inflammatory myositis, and rheumatoid arthritis.