Autoimmune diseases and tolerance

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.

T cell tolerance

- Main contributor to tolerance is **CD4 T cells** because:
  - MHC relation to autoimmune diseases (MHC molecules present peptides (including self-antigens) to T cells. If CD4+ T cells react abnormally to self-antigens presented by MHC, it can lead to autoimmune diseases.)
  - T cell is the **key regulator** of immune response to proteins (the most complicated)
- 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**

Central tolerance

- 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**)
- if they react to the self-antigen they die or differentiated to T reg

AIRE deficient cause:

1. polyendocrinopathy syndrome
2. Addison
3. hypo parathyroid
4. chronic candidiasis

Peripheral tolerance

- Auto-reactive T cells may result because fail of T cell regulation
- Fail of expression of **CTLA-4** after T cell activation. (binds to B7)
- 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. (Prevents excessive T cell activation by promoting inhibition)
- or because presence of **co-stimulatory signals (B7) on APC** in chronic infection the absence of antigen. **Problem**: If the infection resolves and the antigen is no longer present

B lymphocytes tolerance

- **Central**
- Editing, deletion and anergy

  Editing: If a developing B cell recognizes self-antigens, it can rearrange its genes to make a new, non-self-reactive receptor.
  Deletion: Self-reactive B cells are destroyed (apoptosis).
  Anergy: Self-reactive B cells become inactive and unable to respond to antigens.
- **Peripheral**
- absence of specific **helper T cells**, B cells may be rendered functionally **unresponsive or die by apoptosis.**
- Expression of death proteins; **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 like:
  1. Cyclosporin
  2. anti-lymphocytic
  3. antibodies as anti-CD4
  4. soluble CTLA-4
  5. 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 e.g.; post-trauma, exposed antigens of nucleus in SLE (systemic lupus erythematosus) that immune system did not expose to before. epitope spreading.

  Sequestrated antigens refer to self-antigens that are typically hidden from the immune system due to their location in "privileged" sites within the body, such as the eyes, brain, and testes.

- Exposure to **microbial antigens that cross-react** (means immune reaction against antigen other than antigen that presented first) with self-antigens (molecular mimicry); **streppyogenes (Streptococcus 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.**
- 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.
  in chronic inflammation, these immune cells start expressing costimulatory signals even when there is **no infection**. This leads to **bystander activation** — meaning **T cells** are activated **without recognizing their usual target** (no specific antigen). They can attack **healthy cells** by mistake.
- Genetic pre-disposition (Polygenic);
  1. Rheumatoid arthritis (RA) in **HLA DR4**
  2. thyroiditis in **HLA DR5**
  3. multiple sclerosis in **HLA DR2**
  4. systemic lupus erythematosus (SLE) in **HLA DR3**
  5. Type 1 diabetes in HLA **DR3 and 4**
  6. celiac disease **HLA-DQ 2 or HLA-DQ 8**
- Other genetics (single gene),
  1. **loss of Fas, FasL expression**
  2. **CTLA-4 gene mutations(lymphoproliferative)**
  3. **AIRE gene (polyendocrine syndrome)**
  4. **C4 gene (SLE)**
- Hormonal factors, RA and SLE more in females

Gene	Phenotype of Mutant Knockout Mouse	Mechanism of Failure of Tolerance	Human Disease
AIRE	Destruction of endocrine organs by antibodies and lymphocytes	Failure of central tolerance	Autoimmune polyendocrine syndrome (APS)
C4	SLE	Defective clearance of immune complexes; failure of B cell tolerance?	Systemic Lupus Erythematosus (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 linked to 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	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (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

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 islets Beta cells)
- **Gravis** and **Hashimoto thyroiditis** In Graves' disease, the thyroid is overactive (hyperthyroidism).In Hashimoto's thyroiditis, the thyroid becomes underactive (hypothyroidism).

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 the skin epidermis and joint. (cluster plaques on the skin) **(type 4 HS)**

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 mediates (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 are on and off, when it is on it is called **flare up.**
  Symptoms of autoimmune diseases can vary over time. When symptoms become worse or intensify, it is called a flare-up. When symptoms are less noticeable or in remission, the disease is less active.

Lab. Diagnosis

- Elevated levels of immunoglobulins
  High immunoglobulin levels can indicate ongoing immune activation, often seen in autoimmune disorders.
- High CRP, ESR
  High CRP (C-reactive protein) and ESR (Erythrocyte Sedimentation Rate): What it is: CRP and ESR are markers of inflammation in the body. **Why it matters**: Elevated levels of these markers can indicate inflammation associated with autoimmune diseases, especially during flare-ups.
- Auto-antibodies; anti-nuclear (ANA**) systemic lupus erythematosus, Sjogren's syndrome, scleroderma or mixed connective tissue disease.**
- rheumatoid factor (RF) in RA

- Complement levels may decreased. **Decreased complement levels** may be seen in diseases like **SLE**, where complement is used up in immune reactions and inflammation.
- 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. **Plasmapheresis** (also called **plasma exchange**) is a procedure where blood is removed from the body, the **plasma** (which contains harmful antibodies) is separated and discarded, and the remaining blood components are returned to the patient.

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; antiglomerular 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-peroxidase (TPO) antigens (type 2 hypersensitivity)
- hypothyroidism, and hard and large gland due to lymphocytic infiltrate (type 4 hypersensitivity)
- Treatment, thyroid hormone replacement

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** (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 **polydipsia, polyphagia, polyuria**
- Treatment, **insulin therapy, immune therapy** by **induce tolerance to diabetic antigen.**

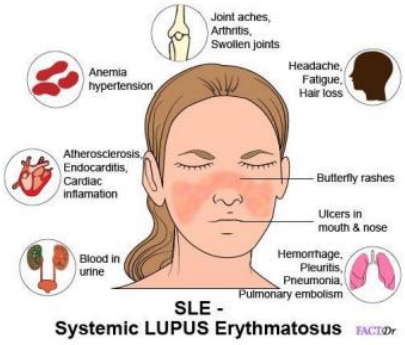
Inflammatory bowel disease

- 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)

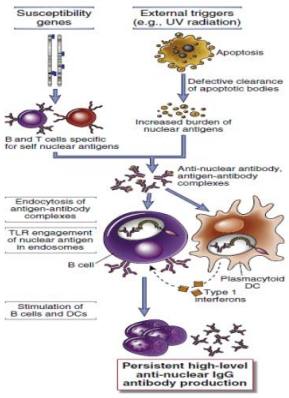
Feature	Crohn's Disease	Ulcerative Colitis
Inflammation Depth	Transmural (affects the entire wall of the intestine)	Confined to mucosa (innermost layer)
Location	Affects any part of the GI tract (mouth to anus)	Primarily affects the colon and rectum
Pattern	Patchy (skip lesions, some parts unaffected)	Continuous (lesions are continuous, starting from rectum)
Complications	Fistulas, strictures	Toxic megacolon

SLE

- Diagnosis
  - Symptoms as **skin rash, proteinuria and edema**
  - Tissue biopsy; immunofluorescence 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**



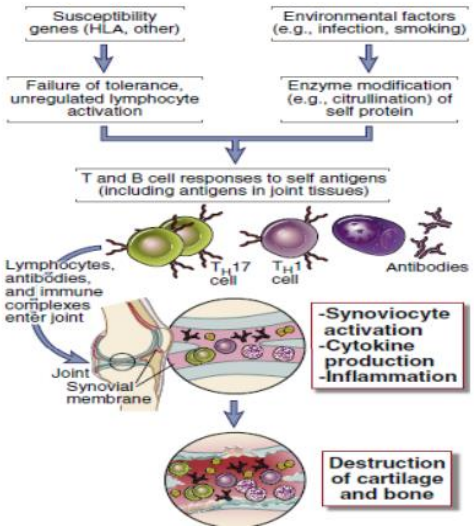
New Therapies for Systemic Lupus Erythematous

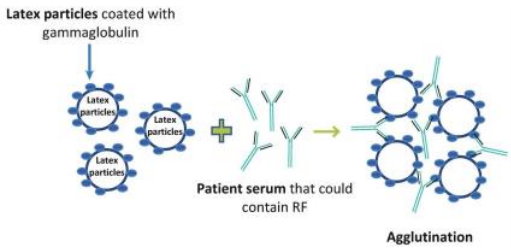


1. **anti-IFN-a antibodies** in the disease
2. **inhibit TLR signals**
3. **depleting B cells** by use of an **antibody against the B cell surface protein CD20.**
4. **antibody that blocks the B cell growth factor BAFF**

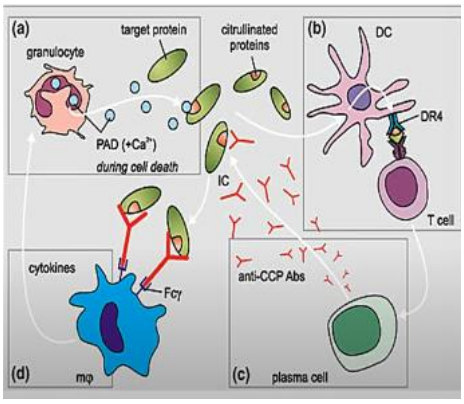
Rheumatoid arthritis

- 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** (tiny synthetic particles) covered with human antibodies **(IgG)**. The latex beads clump or agglutinate if rheumatoid factor is present in-patient serum





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 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

new therapy for RA

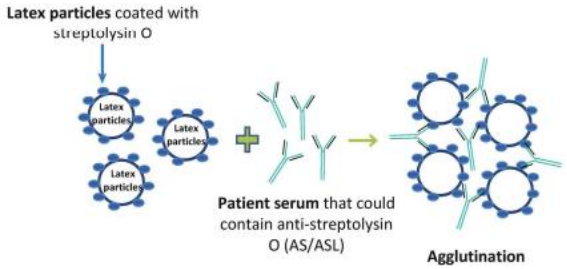
- **TNF Antagonists**: These therapies have transformed the course of the disease, shifting it from progressive joint destruction to manageable chronic inflammation.
- **Targeted Therapies in the Last 5 to 10 Years**: A variety of new therapies have been developed, providing insight into disease pathogenesis.
- **Blockade of Cytokines Other Than TNF**: Effective therapies include:
  - IL-6 receptor blockade (antibody that blocks IL-6 receptor)
  - IL-1 antagonist
  - JAK signaling inhibitors (small molecules inhibiting JAK signaling, an important intracellular mediator for cytokine receptors)
- **T Cell Activation Inhibition**: Accomplished through the blockade of **B7:CD28 co-stimulation** using **CTLA-4-Ig**, a fusion protein consisting of the extracellular domain of CTLA-4 and the Fc portion of IgG, which binds to B7.
- **B Cell Depletion**: **Anti-CD20 antibody** has proven to be effective, although the mechanisms underlying this effect are not fully 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.**



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 **antiU1-ribonucleoprotein, Raynaud phenomenon** (fingers and toes turn white or blue)**, and features of at least 2 connective tissue diseases**, including **systemic lupus erythematosus, systemic sclerosis, inflammatory myositis, and rheumatoid arthritis.**

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