AUTOIMMUNITY
AND
AUTOIMMUNE DISEASES

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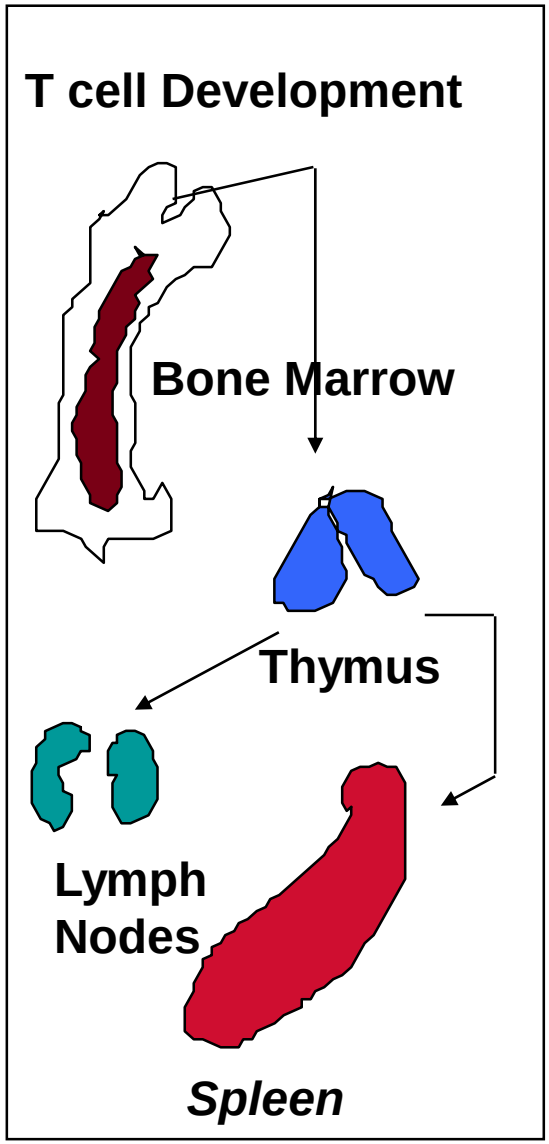


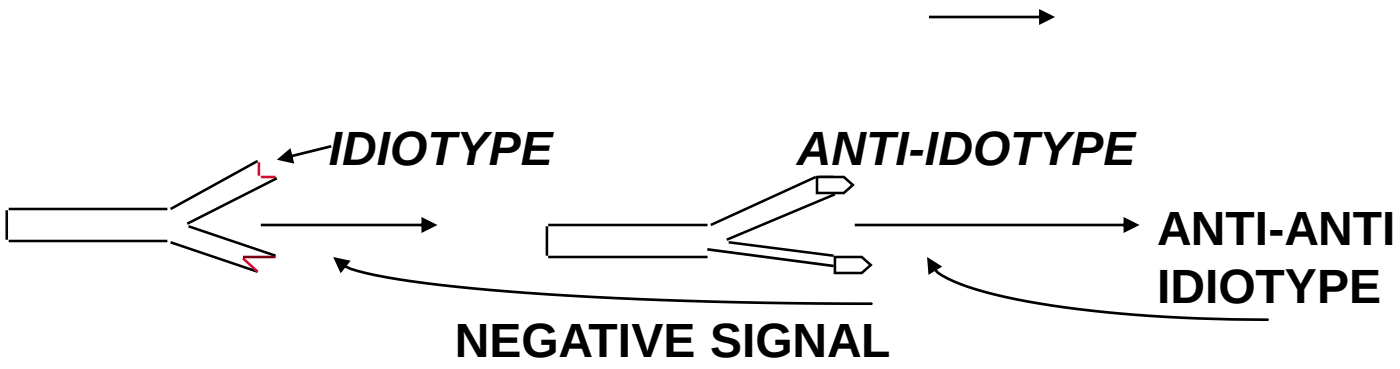
- **HORROR AUTOTOXICUS:** Ehlrich proposed that immune system should not be toxic to auto (self) tissues.
- In normal individuals, majority of lymphocytes reacting with auto-antigens are deleted in primary lymphoid organs by **CLONAL DELETION** (Central Tolerance)
- Few self-reactive lymphocytyes which escape and reach secondary lymphoid tissues are down regulated there by **CLONAL ANERGY, Tregs or other mechanisms** (Peripheral Tolerance)
- **Thus, normal individuals are TOLERANT to AUTO ANTIGENS**

AUTOIMMUNITY: The presence of autoantibodies (antibodies against auto-antigens) or autoreactive (self reactive) lymphocytes without the induction of any pathological changes

Autoantibodies can be found in normal individuals, particularly in old animals and in the female gender group

AUTOANTIBODIES may have a physiological role in:

1. Removal of senescent/ damaged cells
2. Idiotype anti-idiotypes negative feed back



AUTOIMMUNE DISEASES: **Pathological changes (structural and/or functional) in tissues and/or organs as a consequence of autoreactive cells**

CRITERIA FOR AUTOIMMUNE DISEASE OR WITEBSKY'S POSTULATES

1. The presence of autoantibodies or autoreactive lymphocytes (in association with pathological changes)

2. Experimental reproduction of the disease in laboratory animals

3. The features of the experimental disease must closely match with the clinical disease.

4. Ability to passively transfer the disease by autoantibodies or lymphocytes

General Characteristics

- Autoimmunity results from a failure or breakdown of the mechanisms normally responsible for maintaining self-tolerance in B cells, T cells, or both.
- Although underlying molecular etiologies remain elusive for most autoimmune diseases, it is thought that autoimmunity is multifactorial, resulting from a complex interplay between genetic susceptibility, environmental triggers, and aberrant immune regulation
- Autoimmune diseases may be either systemic or organ specific.
- Various effector mechanisms are responsible for tissue injury in different autoimmune diseases.
- It is not uncommon for a patient to have symptoms of more than one autoimmune disease (known as ‘overlap’, or undifferentiated collagen vascular syndrome).
- On contrary, a patient with one autoimmune disease may have serologic markers – but no clinical manifestations – of another

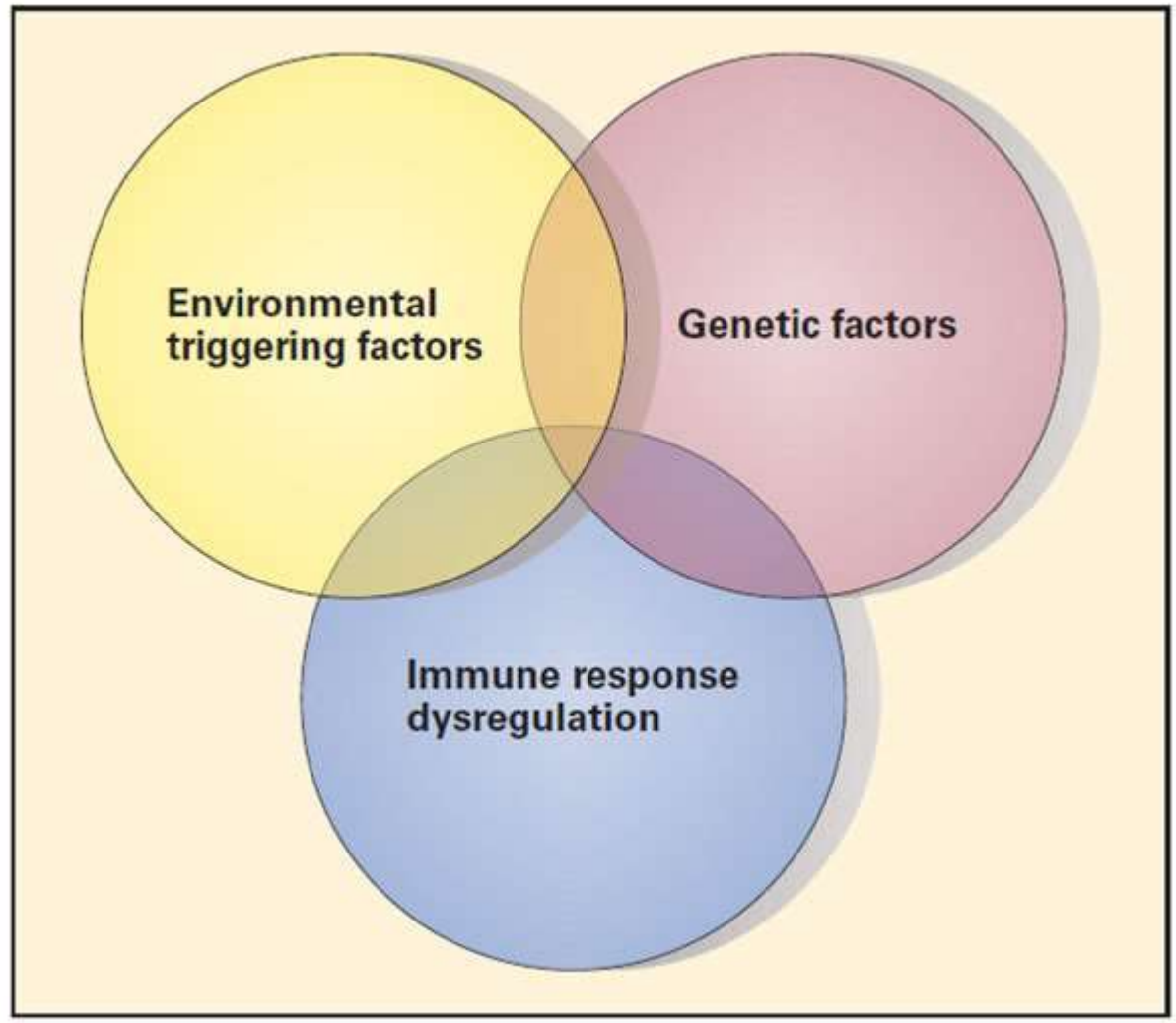
What Causes Autoimmune Diseases?

The Mosaic of Autoimmunity

- The exact etiology of autoimmune diseases still remains unknown.
- Several factors are presumed to contribute to the emergence of an autoimmune disease in a host, which are:
  - the genetic predisposition,
  - the environmental triggers such as bacterial (including the gut microbiota), viral, fungal and parasitic infections; physical and environmental agents; hormonal factors, and
  - the hosts immune system dysregulation.

Shoenfeld et al. (1989) coined the term "The Mosaic of Autoimmunity" to include all these factors interplay.

The Three Etiopathogenic Factors Involved In Autoimmune Diseases.



(Bellanti JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012].)

Possible Reasons of Autoimmune Diseases

- **Genetics** - Certain autoimmune disorders are familial. Many autoimmune diseases are associated with MHC-I or II, including ankylosing spondylitis (HLA-B27), SLE (HLA-DR2, DR3), RA (HLA-DR4), type 1 DM (HLA-DR3, DR4), and MS (HLA-DR2). Gene mutations may also result in risk of autoimmune disorders
- **Escape of auto-reactive clones:** The negative selection in the thymus may not be fully functional to eliminate self reactive cells. Not all self antigens may be represented in the thymus or certain antigens may not be properly processed and presented.
- **Abnormal expression of class II antigens** - Class II antigens begin to be expressed on cells that normally do not bear these antigens. Eg. Epithelial cells of the thyroid and salivary glands.
- **Sex** - Most autoimmune diseases such as Lupus, primarily affect women; estrogen promotes autoimmunity
- **Defective apoptosis and impaired Treg activity-** For example, Autoimmune polyendocrine syndrome type I (APSI) or (APECED) due to defects in AIRE induced apoptosis in central tolerance and Immune dysregulation, polyendocrinopathy, enteropathy (X-linked) (IPEX) syndrome due to Foxp3 mutation leading to and absence of Treg

Association of autoimmune diseases and MHC

MHC-I association
Ankylosing spondylitis (HLA-B27)
Reactive arthritis (HLA-B27)
Psoriasis (HLA B-13, B-16, B-17)
MHC-II association
Systemic diseases
Systemic lupus erythematosus (HLA-DR2 and DR3)
Rheumatoid arthritis (HLA-DR4)
Organ-specific diseases
Type 1 diabetes mellitus (HLA-DR3 and DR4)
Multiple sclerosis (HLA-DR2)

Possible Reasons of Autoimmune Diseases

- **Exposure of hidden (sequestered) antigens or new epitopes**
  - Lymphoid cells may not be exposed to some self-antigens during their differentiation, because they may be late-developing antigens (new epitopes) or may be confined to specialized organs (sequestered antigens).
  - A release of such antigens from these organs, resulting from accidental traumatic injury or surgery, can result in the stimulation of an immune response and initiation of an autoimmune disease.
  - Examples are intracellular antigens (e.g. DNA, mitochondria), band-3" protein on senescent RBC, eye lens, spermatozoa, Rheumatoid factor (eg. Rheumatoid arthritis).

Possible Reasons of Autoimmune Diseases

- **Cross-reactivity with microorganisms (Molecular mimicry)**

Antigens on certain pathogens may have determinants which cross react with self antigens and an immune response against these determinants may lead to effector cells or antibodies against tissue antigens.

Streptococci ("A" group)	Cardiac Myosin, Kidneys
Treponema pallidum	Cardiolipin
Leptospira	Corneal tissue
Mycoplasma	Lung tissue
Trypanosoma cruzii	Neurons and cardiac muscle

Molecular mimicry has been proposed as a cause of the autoimmune phenomena observed in COVID-19; three human proteins (DAB1, AIFM, and SURF1) that are present in neurons of the respiratory pacemaker in the brainstem share potentially antigenic epitopes with SARS-CoV-2,

Possible Reasons of Autoimmune Diseases

- **Viral involvement**
  - Retroviral infection in Sjogren's syndrome (Dry eye / Dry mouth) and in Systemic lupus erythematosus (a multi-organ disease).
  - Epstein-Barr virus infection and Systemic lupus erythematosus
  - Coxsackie viral infection in type I diabetes

***Possible mechanisms*:**

- **Molecular mimicry -** HCV and platelet glycoprotein IIIa (ITP)
- Interference with the regulatory control mechanisms - "bystander activation" whereby the infection may lead to activation of APCSs that may in turn activate pre-primed auto-reactive T-cells, leading to the production of pro-inflammatory mediators, which in turn may lead to tissue damage
- **Epitope spreading:** Autoimmune reactions initiated against one self antigen that injure tissues may result in the release and alterations of other tissue antigens, activation of lymphocytes specific for these other antigens, and exacerbation of the disease.
- **Induction of new antigens**
- **Polyclonal B cell activation**

Mechanisms of Tissue Damage in Autoimmune Diseases

AUTOIMMUNE DISEASES

Types of Autoimmune reactions

1. Autoantibodies against self-components
2. Antigen-antibody immune complexes deposit in organs
3. Autoreactive T cells against self-components
4. Combinations of above

Mechanisms of issue damage

- Mechanisms involved in tissue damage are very complex.
- In a number of autoimmune diseases more than one mechanism are involved.
- **IgE autoantibodies (Type I):** Rare. A possible example: “Milk allergy” in Jersey cattle; IgE autoantibody response to α-casein.
- **Cytotoxic (Type II):**

  Autoantibodies to cell surface, e.g.

  RBC.....autoimmune hemolytic anemia

  Thrombocytes..... autoimmune thrombocytopenia
- **Immunecomplex (Type III)**:

  Autoantibodies (Ab) + Antigen (Ag) $\longrightarrow$ [Ab-Ag] Immunecomplex, e.g. SLE, RA
- **T-Cell Mediated Damage (Type IV):**

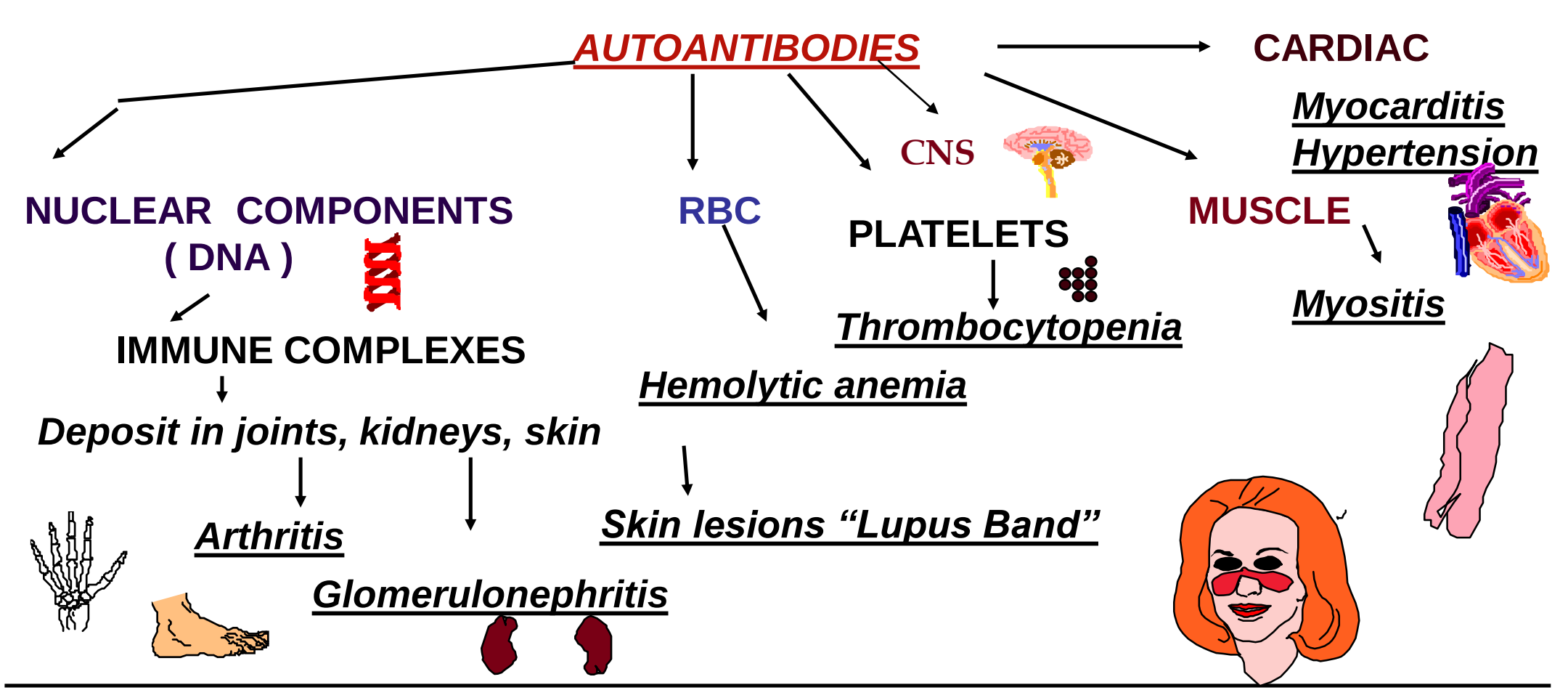
  T cells are primarily involved in tissue damage, e.g. autoimmune thyroiditis, ulcerative colitis, Insulin-dependent Juvenile-onset Diabetes, autoimmune encephalitis

Mechanisms of Tissue damage

- T cells are involved in almost all autoimmune diseases, particularly in organ specific autoimmune disorders (probably due a lack of T regulatory cells or the participation of Th17 cells).
- Macrophages, which are activated by T cells are also involved in tissue damage (release of toxic enzymes and oxidative free-radicals; Type IV).
- Most autoimmune diseases are characterized by the production of antibodies directed to self antigens, known as **auto-antibodies**
- The physical properties of an autoantibody that determines its pathogenicity include:
    - its affinity to the antigen that plays a role in immune complexes formation, and
    - its charge that helps antibody attach to tissues, e.g. in SLE, positively charged auto-antibodies (anti-double stranded DNA) associate with the negatively charged basement membrane in the kidney, where they can form complexes in situ with DNA and lead to local inflammation.
- Most of the pathogenic auto-antibodies are of IgG isotype.

Auto Antibodies in Autoimmune Disorders

Disease	Mechanism	Clinical Picture
AUTO ANTIBODIES TO RECEPTORS		
Myasthenia Gravis	Auto Abs to Ach receptors at NMJ	Blockage of NM J transmission and **muscular weakness**
Graves' disease	Auto Abs to receptors for TSH	Increased release of TH resulting in **hyperthyroidism**
AUTO ANTIBODIES TO ORGAN CELLS		
Hashimoto's disease	Auto Abs and Auto reactive T cells to thyroglobulin and thyroid microsomal Ag	Destruction of thyroid gland resulting in **hypothyroidism**
Type I Diabetes Melitus	Auto Abs and Auto reactive T cells to pancreatic islet cells	Destruction of islet cells and failure of insulin production resulting in **hypothyroidism**
AUTO ANTIBODIES TO CELLULAR MOLECULE		
S.L.E.	Auto Abs to nuclear Ag such as DNA. Formation of DNA-anti-DNA IC	Deposition of IC in multiple organs
Rheumatoid Arthritis (RA)	Auto Abs to CCP + IgG (Rheumatoid Factor – RA Ag) and Auto reactive T cells. Formation of IC.	Deposition of IC in joints resulting in inflammation and destruction of cartilage and bone



SUSPECT SLE IN AN ANIMAL WITH MULTIPLE ABNORMALITIES

(TOGETHER WITH POSITIVE SEROLOGY

eg. anti-nuclear antibodies and/or anti-DNA antibodies)

Examples of diseases caused by cell and tissue specific antibodies

Disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb:IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture's syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor-mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

Examples of T cell-mediated Immunological diseases

Disease	Specificity of pathogenic T cells	Human disease	Animal models
Type I (insulin-dependent) diabetes mellitus	Islet cell antigens (insulin, glutamic acid decarboxylase, others)	Yes; specificity of T cells not established	NOD mouse, BB rat, transgenic mouse models
Rheumatoid arthritis	Unknown antigen in joint synovium	Yes; specificity of T cells and role of antibody not established	Collagen-induced arthritis, others
Multiple sclerosis, experimental autoimmune encephalomyelitis	Myelin basic protein, proteolipid protein	Yes; T cells recognize myelin antigens	EAE induced by immunization with CNS myelin antigens; TCR transgenic models
Inflammatory bowel disease (Crohn's, ulcerative colitis)	Unknown	Yes	Colitis induced by depletion of regulatory T cells, knockout of IL-10
Peripheral neuritis	P2 protein of peripheral nerve myelin	Guillain-Barre syndrome	Induced by immunization with peripheral nerve myelin antigens
Autoimmune myocarditis	Myocardial proteins	Yes (post-viral myocarditis); specificity of T cells not established	Induced by immunization with myosin or infection by Coxsackie virus

Types of Autoimmune Diseases

Autoimmune Diseases

ORGAN SPECIFIC

- AUTOIMMUNE THYROIDITIS
- AUTOIMMUNE SKIN DISEASES
- AUTOIMMUNE REPRODUCTIVE DISEASES
- AUTOIMMUNE HEMOLYTIC ANEMIA
- MYESTHENIA GRAVIS
- AUTOIMMUNE OPTHALMIC DISEASES
- INSULIN-DEPENDENT DIABETES
- AUTOIMMUNE ADRENALITIS
- AUTOIMMUNE NEUROLOGICAL DISEASES

NON-ORGAN SPECIFIC

- SLE
- RHEUMATOIDARTHRITIS
- POLYARTHRITIS (NON-RA)
- DERMATOMYOSITIS
- MULTIPLE SCLEROSIS

POSSIBLE AUTOIMMUNE

- Alopecia atrea
- STEROID RESPONSIVE MENINGITIS

Organ specific and non-organ specific disorders

	organ specific	non-organ specific
antigen	essentially localized to given organ	widespread throughout the body
lesions	antigen in organ is target for immunological attack	complexes deposit systemically particularly in kidneys, joints and skin
overlap	with other organ-specific antibodies and diseases	with other non-organ specific antibodies and diseases

Organ Specific Autoimmune Diseases

Organ-specific autoimmune diseases

- The immune response is directed against a unique antigen in a given organ.
- Cells may be damaged by **humoral** and/or **cell mediated** effector mechanisms.
- **Antibodies** may over-stimulate or blocks the normal function of the target organ.

AUTOIMMUNE REPRODUCTIVE DISEASES

- **ORCHITIS: WITH ANTI-SPERM AUTOANTIBODIES**

  Autoantibodies to sperm antigens will agglutinate the sperms - ***Decreased Fertility***

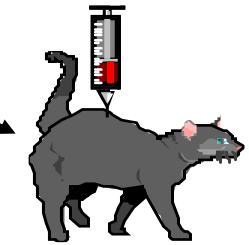
- **AUTOANTIBODIES TO HORMONES** - Progesterone, Estrogen, LH, GnRH

"IMMUNOLOGICAL CONTRACEPTION" (Non-Surgical Contraception)

BOVINE
OVINE
LH

Antibodies cross react with Feline LH

GnRH



Antibodies cross react with Feline GnRH

Net result: Sterility

Female DOG

Infertility

Protein from zona pellucida of Ovary

MYAESTHENIA GRAVIS - It is a disorder of signal transmission between the nerves and muscles, which is characterized by muscular weakness and excessive fatigue. MG occurs due to formation of autoantibodies to acetylcholine receptor. The antibodies, which are of IgG type, initiate a complement mediated lysis of muscle cells. In dogs, cats and humans this disorder is either congenital or acquired . In any breed of Dog, the disease can develop, but German shepherds, Golden retrievers, and Labradors appear to be more susceptible to the disease. Disease can be classified as focal myasthenia gravis and generalized myasthenia gravis. In focal MG, an animal presents with mega esophagus and various degrees of facial paralysis with limb muscle weakness. In generalized MG, limb muscle weakness is associated with facial paralysis and mega esophagus.

AUTOIMMUNE OPTHALMIC DISEASES

Equine recurrent uveitis - periodic ophthalmia/moon blindness in horses. The inciting factors in horses include microbial agents such as Leptospira spp.. Inter-photoreceptor retinoid binding protein is the major autoantigen involved, with subsequent epitope spreading to the S. protein. Affected animals (horses) have circulating antibodies to L. interrogans, recurrent attacks of uveitis, retinitis, and vasculitis. They have blepharospasms, lacrimation and photophobia in severe cases. The eye lesions are infiltrated with Th-1 cells and neutrophils with extensive fibrin and C3 deposition

AUTOIMMUNE HEMOLYTIC ANEMIA (AHIA)

- AHIA is characterized by production of auto-antibodies against red blood cell antigens resulting in their destruction.
- The disease is reported from humans, dogs, cattle, horses, cats, mice, rabbits.
- It can occur independently or in association with SLE or thrombocytopenia with Feline Leukemia.
- The autoantibodies are produced against red cell glycophorins, cytoskeletal protein spectrin and the membrane anion exchange protein (CD 233 or band 3) in case of dogs.
- The destruction of red blood cells may result from either intra vascular hemolysis that is mediated by compliment or by the removal of antibody coated red cells by the macrophages of spleen and liver.
- The cause of red cell destruction is the alteration in red cell surface antigens (neo-antigens) that is induced by drugs and viruses.
- Its onset may be associated with other immunological abnormalities, with stress (vaccination), viral diseases, or with hormonal imbalances (pregnancy or pyometra).

AUTOIMMUNE HEMOLYTIC ANEMIA

Types	Mechanisms of RBC destruction
"Warm" autoantibodies	IgG antibodies to Rh (37º). Detected by Coombs' test. Complement not activated. RBC cleared by RES.
"Cold" autoantibodies	IgM antibodies to I or i (<37ºC). Complement activated. RBC lysis at cold temperature.
"Drug induced" antibodies	Penicillin hapten binds to RBC antigen. Antibodies form to hapten-protein complex. RBC lysis or cleared by RES.

Type I Diabetes Melitus (TIDM)

- Autoimmune type 1 diabetes mellitus (T1DM) is a multi-stage disease of undetermined aetiology characterised by an aggressive and selective autoimmune response against β-cells of islets of Langerhans of pancreas.
- Genetic factors include both MHC and non-MHC genes.
- The most common environmental factors are viral infections (such as CMV and Coxsackie) and vitamin D deficiency.
- Three major auto-antigens have been identified in T1DM: insulin, GAD65 and IA2.
- T1DM is primarily a cell-mediated autoimmune disease.
- The CD8+ auto-reactive Tlymphocytes are the most abundant and the most active in β-cell destruction.
- The islet autoantibodies are predictive markers of an ongoing autoimmune response, yet their exact role in beta cell destruction remains to be clarified.

Organ-specific autoimmune diseases

Disease	Main organ affected	Proposed self-antigen(s)	Clinical presentation
Organ-specific autoimmune diseases			
Multiple sclerosis	Central nervous system	Myelin basic protein, myelin oligodendrocyte protein	Loss of vision, weakness of limbs, sensory abnormalities, incontinence
Sympathetic ophthalmia	Eye	Various uveal antigens	Eye pain, loss of vision, sensitivity to light
Graves' disease	Thyroid	Thyrotropin receptor	Hyperthyroidism (weight loss, nervousness, palpitations, diarrhea), exophthalmos
Hashimoto's thyroiditis	Thyroid	Thyroperoxidase, thyroglobulin	Hypothyroidism (weight gain, constipation, skin changes, myxedematous dementia)
Goodpasture's syndrome	Lung, kidney	Glomerular basement membrane (type IV collagen)	Kidney and respiratory insufficiency
Pernicious anemia	Stomach	Intrinsic factor	Anemia, gastritis
Crohn's disease *	Intestine	? microbial antigens	Hemorrhagic diarrhea, abdominal pain, draining fistulas
Ulcerative colitis *	Large intestine	? microbial antigens	Hemorrhagic diarrhea, abdominal pain
Diabetes mellitus type I	Pancreas	Islet cell, insulin, glutamic acid decarboxylase (GAD)	Polyphagia, polyuria, polydipsia, weight loss
Immune thrombocytopenia	Platelets	Glycoproteins on the surface of platelets	Easy bruising, hemorrhage
Myasthenia gravis	Muscle	Acetylcholine receptor	Muscle weakness, fatiguability
Hemolytic anemia	Red cells	I antigen	Anemia

Non-organ Specific or Systemic Autoimmune Diseases

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- SLE is an autoimmune disease characterized by multi-organ inflammation, with a diverse array of clinical manifestations and production of pathogenic auto antibodies directed against nucleic acids.
- The exact patho-aetiology of SLE remains elusive. Defective clearance of apoptotic cells and immune complexes, are important contributors to the development of SLE.
- Aberrant innate immune responses also play a significant role in the pathogenesis of SLE.
- The central immunological disturbance in patients with SLE is autoantibody production
- The basic pathological features of SLE are inflammation and blood vessel abnormalities, which include band or occlusive vasculopathy, vasculitis, and immune complex deposition.
- The most characterized organ pathology is in the kidney.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

DOGS, CATS AND HORSES

MULTI-ORGAN INVOLVEMENT:
Kidneys, Joints, Skin, Salivary Glands, Hemopoetic cells etc.

B cell Hyperactivity
Abnormalities in T cells
Decreased regulatory T cells

Possible involvement of infectious agents:

- **Epstein- Barr virus (EBV)**
- **Parainfluenza**
- **Measles**
- **Myxovirus**
- **Retrovirus**

Rheumatoid arthritis (RA)

- Rheumatoid arthritis (RA) is a common autoimmune disease affecting approximately 1% of the world's population.
- It is also observed in dogs (especially small), cats and horses.
- RA disease is characterized by a symmetric, polyarthritis of the small joints of the hands and feet, but almost any joint can become involved.
- Affects not only joints but also other parts of the body .
- Pathologically, the synovial tissue becomes hypertrophied, highly vascularized, and infiltrated with leukocytes, principally macrophages
- The proliferating fibroblasts and infiltrating macrophages, develops into an inflammatory mass, termed the pannus.
- The synovia proliferates and release destructive proteolytic enzymes, which cause erosion and dectruction of cartilage and bone.
- The subsynovial area is comprised of infiltrating macrophages and dendritic cells and lymphocytes.

Rheumatoid arthritis (RA)

- The precise cause of RA is unknown but genetic, epigenetic and environmental factors are involved.
- Possible infections: *Mycobacteria,* Lyme's Disease, Parvovorus*, Mycoplasma,* EBV
- **Possible autoantigens:**
  - (1) Rhuematoid factor: IgM antibody against an abnormally glycosylated IgG .
  - (2) Type II- Collagen
- Macrophages have been most clearly implicated in pathogenesis and are the major synovial producers of TNF-α. Other cells include:
  - neutrophils, present in the synovial fluid, synthesize inflammatory PGs, proteases, and ROS.
  - Mast cells release cytokines, chemokines, proteases, and vasoactive amines.
- It is hypothesised that a T-cell dependent inflammatory reaction to an unknown antigen underlies the pathology (Th1 and ?Th17)

Systemic autoimmune diseases

Disease	Main organ affected	Proposed self-antigen(s)	Clinical presentation
Sjögren's syndrome	Salivary and lacrimal glands	Nuclear antigens (SSA, SSB)	Dry eyes, dry mouth, lung and kidney disease
Rheumatoid arthritis	Joints, lung, nerves	Citrulinated peptides in the joint, IgG	Deforming arthritis, skin nodules, occasional lung and nerve involvement
Wegener's granulomatosis	Lung, kidney	Proteinase 3 (c-ANCA)	Sinusitis, shortness of breath, kidney failure
Systemic lupus erythematosus	Kidney, skin, joints, central nervous system	DNA, histones, ribonucleoproteins	Arthritis, skin rashes, kidney insufficiency, nerve damage

Treatment of autoimmune diseases

Available treatment thus far is non-specific

In the early course of the disease (e.g. RA) Asprin **or steroidal and Non-steroidal anti-inflammatory drugs (NSAID)**

IMURAN (AZATHIOPRINE)
CORTICOSTEROIDS
GOLD SALTS (e.g. Auranofin)

Monoclonal Antibodies – e.g. Rituximab for MS, Belimumab for anti-phospholipd Ab

EXPERIMENTAL APPROACHES:

- Bone Marrow Transplantation
- Stem cell therapy
- Intravenous immunoglobulin therapy
- Fab ANTIBODIES FRAGMENTS TO T and B cells
- Anti- CD4, B cells OR Anti- IL-2 RECEPTOR antibodies
- ***Pentraxin 3*** – a humoral soluble PRR
- ***Antigen-based immunotherapy*** - overloading the immune system by gradual but ever-increasing doses of the same molecule that it is attacking to make reactive T cells tolerant (T cell switching)