AUTOIMMUNITY
AND
AUTOIMMUNE DISEASES

RAKESH SHARDA
Department of Veterinary Microbiology
NDVSU College of Veterinary Science & A.H.,
MHOW
- **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 lymphocytes 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 feedback
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 (APS1) 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

<table>
<thead>
<tr>
<th>MHC-I association</th>
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<tbody>
<tr>
<td>Anykylosing spondylitis (HLA-B27)</td>
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<tr>
<td>Reactive arthritis (HLA-B27)</td>
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<tr>
<td>Psoriasis (HLA B-13, B-16, B-17)</td>
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</table>

<table>
<thead>
<tr>
<th>MHC-II association</th>
</tr>
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<tbody>
<tr>
<td>Systemic diseases</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (HLA-DR2 and DR3)</td>
</tr>
<tr>
<td>Rheumatoid arthritis (HLA-DR4)</td>
</tr>
<tr>
<td>Organ-specific diseases</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus (HLA-DR3 and DR4)</td>
</tr>
<tr>
<td>Multiple sclerosis (HLA-DR2)</td>
</tr>
</tbody>
</table>
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
- **Immune complex (Type III):**
  - Autoantibodies (Ab) + Antigen (Ag) → [ Ab-Ag ] Immune complex, 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

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

NUCLEAR COMPONENTS (DNA)

IMMUNE COMPLEXES

RBC

PLATELETS

Hemolytic anemia

Deposit in joints, kidneys, skin

Arthritis

Glomerulonephritis

Skin lesions “Lupus Band”

Thrombocytopenia

CNS

CARDIAC

Myocarditis

Hypertension

MUSCLE

Myositis

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target antigen</th>
<th>Mechanisms of disease</th>
<th>Clinicopathologic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Erythrocyte membrane proteins (Rh blood group antigens, I antigen)</td>
<td>Opsonization and phagocytosis of erythrocytes</td>
<td>Hemolysis, anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Platelet membrane proteins (gpIIb:IIIa integrin)</td>
<td>Opsonization and phagocytosis of platelets</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Proteins in intercellular junctions of epidermal cells (epidermal cadherin)</td>
<td>Antibody-mediated activation of proteases, disruption of intercellular adhesions</td>
<td>Skin vesicles (bullae)</td>
</tr>
<tr>
<td>Vasculitis caused by ANCA</td>
<td>Neutrophil granule proteins, presumably released from activated neutrophils</td>
<td>Neutrophil degranulation and inflammation</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli</td>
<td>Complement- and Fc receptor-mediated inflammation</td>
<td>Nephritis, lung hemorrhage</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen</td>
<td>Inflammation, macrophage activation</td>
<td>Myocarditis, arthritis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Antibody inhibits acetylcholine binding, down-modulates receptors</td>
<td>Muscle weakness, paralysis</td>
</tr>
<tr>
<td>Graves’ disease (hyperthyroidism)</td>
<td>TSH receptor</td>
<td>Antibody-mediated stimulation of TSH receptors</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor</td>
<td>Antibody inhibits binding of insulin</td>
<td>Hyperglycemia, ketoacidosis</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Intrinsic factor of gastric parietal cells</td>
<td>Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}</td>
<td>Abnormal erythropoiesis, anemia</td>
</tr>
</tbody>
</table>
# Examples of T cell-mediated Immunological diseases

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

**ORGAN SPECIFIC**
- Autoimmune Thyroiditis
- Autoimmune Skin Diseases
- Autoimmune Reproductive Diseases
- Autoimmune Hemolytic Anemia
- Myesthenia Gravis
- Autoimmune Ophthalmic Diseases
- Insulin-Dependent Diabetes
- Autoimmune Adrenalitis
- Autoimmune Neurological Diseases

**NON-ORGAN SPECIFIC**
- SLE
- Rheumatoid Arthritis
- Polyarthritis (Non-RA)
- Dermatomyositis
- Multiple Sclerosis

**POSSIBLE AUTOIMMUNE**
- Alopecia atrea
- Steroid Responsive Meningitis
<table>
<thead>
<tr>
<th></th>
<th>organ specific</th>
<th>non-organ specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>antigen</td>
<td>essentially localized to given organ</td>
<td>widespread throughout the body</td>
</tr>
<tr>
<td>lesions</td>
<td>antigen in organ is target for immunological attack</td>
<td>complexes deposit systemically particularly in kidneys, joints and skin</td>
</tr>
<tr>
<td>overlap</td>
<td>with other organ-specific antibodies and diseases</td>
<td>with other non-organ specific antibodies and diseases</td>
</tr>
</tbody>
</table>
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 block 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)

**NET RESULT: Sterility**
**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

<table>
<thead>
<tr>
<th>Types</th>
<th>Mechanisms of RBC destruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Warm” autoantibodies</td>
<td>IgG antibodies to Rh (37°C). Detected by Coombs’ test. Complement not activated. RBC cleared by RES.</td>
</tr>
<tr>
<td>“Cold” autoantibodies</td>
<td>IgM antibodies to I or i (&lt;37°C). Complement activated. RBC lysis at cold temperature.</td>
</tr>
<tr>
<td>“Drug induced” antibodies</td>
<td>Penicillin hapten binds to RBC antigen. Antibodies form to hapten-protein complex. RBC lysis or cleared by RES.</td>
</tr>
</tbody>
</table>
Type I Diabetes Mellitus (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 T lymphocytes 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

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

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