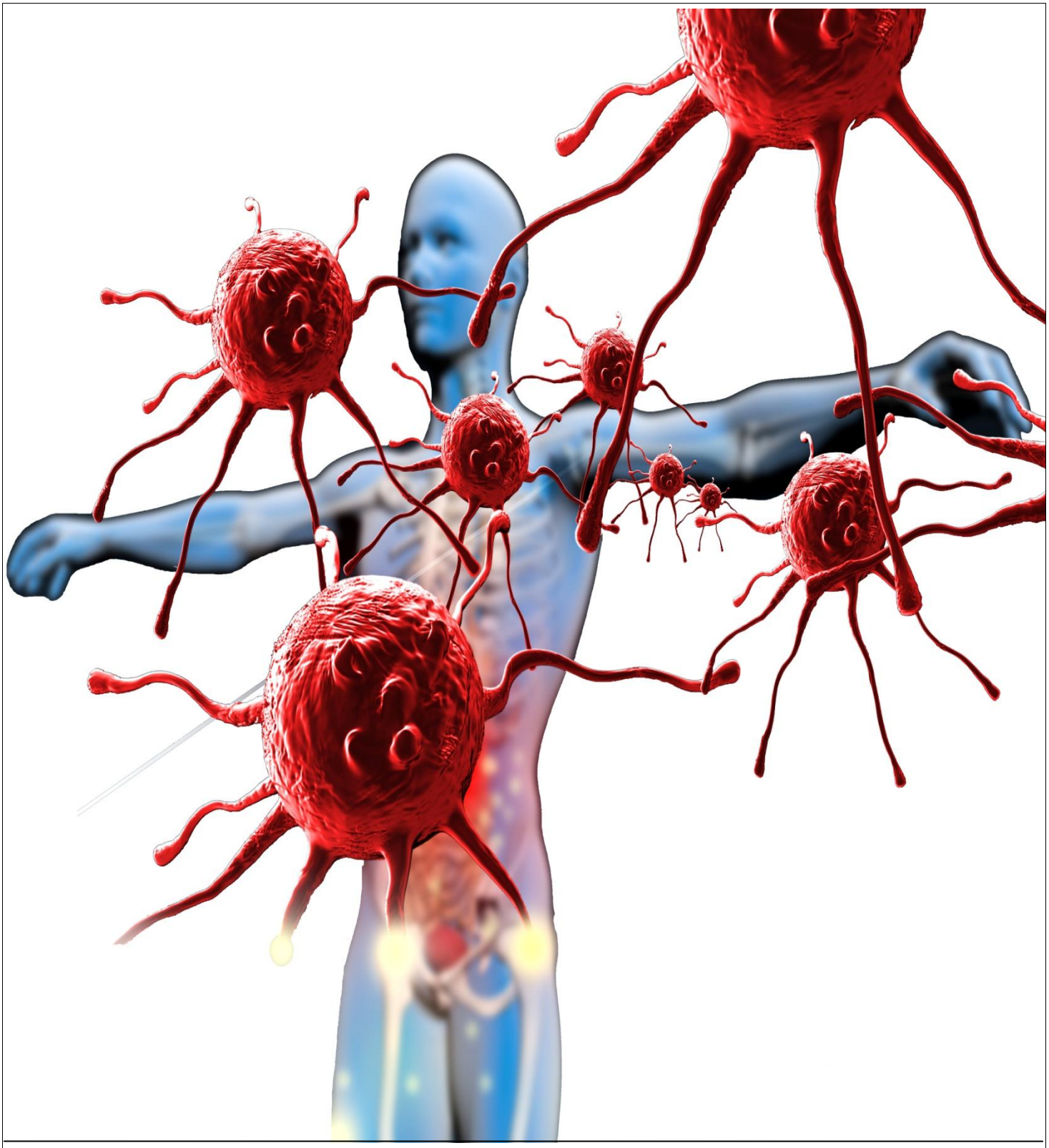

IMMUNOLOGY

Handout 5- Autoimmune Diseases #

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Autoimmunity :

Autoantibodies are a normal phenomenon, IgM of low affinity and multiple specificities (do not depend on foreign antigen for production). No pathological action, function may be :

a)- eliminate degraded autoantigens.

b)- Cross react with foreign antigens (head start, innate immunity).

c)- blind environmental epitopes that may cross react with autoantigens thus protecting against autoimmunity.

These antibodies may not have a function at all and represent antibodies released from anergic (self reactive) B cells when they die. They are produced by CD5 +ve B cells.

In autoimmune disease the antibodies are IgG and are involved in the production of pathology.

Spectrum of autoimmune disease :

Organ specific ---------- Centre ---------- Systemic A.I. disease.

Hashimoto's disease 1ry biliary cirrhosis S.L.E.

Patients are more prone to cancer (organ) or lymphoreticular.

Background of autoimmunity :

1)- Genetic :

Family aggregation of disease, 50% concordance in identical twins, more than in dizygotic twins 5%, and more than siblings with identical HLA haplotypes, which indicates that there is more to it than HLA genes (or HLA linkage). For example C1 and C2 and C4 deficiencies predispose to auto-immune disease.

In animals there are breeds that are genetically prone to disease e.g. NZ BW mice and SLE.

2)- Sex :

Females : SLE, worsens during pregnancy, effect of oestrogen (promotes antibody production).

Males : ankylosing spondylitis (which is believed to be autoimmune).

Some like IDDM affect men and women equally.

3)- Environment :

The lack of 100% concordance in identical twins indicates the presence of other factors.

Diet (RA), sunshine (SLE), Goodpasture (solvents).

Microbes : Rh fever, very slow growing mycobacteria, unidentified viruses.

Reactive arthritis associated with Chlamydiae and Salmonella infections.

The inflammatory process may induce the presentation of self antigens in an immunogenic form.

The autoimmune process is driven by antigen, IgM switches to IgG with somatic mutation and high affinity production.

The auto-immune response is identical to adaptive immunity, cells and antibodies are involved, and the same mechanisms as in infection are involved and result in the tissue damage e.g. complement, neutrophils, macrophages, lymphocytes etc.

Mechanisms of autoimmunity :

1)- Modification of autoantigen :
Drug hapten, somatic mutation, adjuvant presence.

2)- Polyclonal activation of B cells : LPS, EBV.
of T cells : Superantigens.

3)- Molecular mimicry :

4)- Sequestration of antigen : Sperm and lens. BRAIN

5)- Loss of suppression : thymectomy 2-4 days after birth in mice results in AI disease,
AI disease more common in old (tired immune system).
The AIRE gene in medullary thymic epithelial cells. IPEX (FOXP3 MUTATION)

6)- Idiotypic networks :
Virus interacts with receptor X, anti-virus is image of receptor, anti-idiotype interacts with receptor X.

7)- Aberrant expression of MHC II molecules on non-APC in tissues may induce autoimmunity. (gamma interferon).
There is no need for a second signal if large amounts of cytokines were produced during a prolonged infection, probably because the naive T cells become primed by this excessive cytokine production.

8)- Left handedness has been asssociated with some AI disease !

Examples of auto-immune diseases :
Organ and system diseases.

Pernicious anaemia : anti-parietal cell antibody, anti intrinsic factor antibodies.
Rheumatoid arthritis : rheumatoid factor Igm anti-IgG antibody, cell mediated autoimmunity.
Diabetes mellitus : anti-insulin antibodies, cell mediated, anti islet antibodies.
Hashimoto s thyroiditis : anti-thyroglobulin antibodies, anti-microsomal (peroxidase) antibodies.
Graves disease : anti TSH receptor antibodies, anti-peroxidase antibodies.
Multiple sclerosis : cell mediated TH17, anti myelin antibodies.
SLE : assortment of antibodies.
Myasthenia gravis : anti-acetylcholine receptor antibodies.

DISEASE ASSOCIATION WITH MHC MOLECULES

Table 18–4. Examples of T Cell–Mediated Immunologic Diseases

Disease	Specificity of pathogenic T cells	Human disease	Animal models
Insulin-dependent (type I) 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 (EAE)	Myelin basic protein, proteolipid protein	Yes; T cells recognize myelin antigens	EAE is induced by immunization with CNS myelin antigens; TCR transgenic models
Peripheral neuritis	P2 protein of peripheral nerve myelin	Guillain-Barré syndrome	Induced by immunization with peripheral nerve myelin antigens
Experimental autoimmune myocarditis	Myosin	?	Induced by immunization with myosin

Abbreviations: CNS, central nervous system; NOD nonobese diabetic; TCR, T cell receptor.

In some autoimmune diseases such as myasthenia gravis, the lesions are caused by autoantibodies but the disease may be transferred in experimental models by helper T cells specific for self antigens. In such disorders, the function of the T cells is to stimulate the production of autoantibodies.

Table 18–5. Examples of HLA-Linked Immunologic Diseases

Disease	HLA allele	Relative risk*
Rheumatoid arthritis	DR4	4
Insulin-dependent diabetes mellitus	DR3 DR4 DR3/DR4 heterozygote	5 5–6 25
Multiple sclerosis	DR2	4
Systemic lupus erythematosus	DR2/DR3	5
Pemphigus vulgaris	DR4	14
Ankylosing spondylitis	B27	90–100

*Relative risk is defined as the probability of development of a disease in individuals with a particular HLA allele versus individuals lacking that HLA allele. The numbers given are approximations.

Table 18–2. Examples of Diseases Caused by Cell- or 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

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

Table 18–3. Examples of Human Immune Complex–Mediated Diseases

Disease	Antigen involved	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Serum sickness	Various proteins	Arthritis, vasculitis, nephritis