# مقدمة في علم المناعة الطبّي

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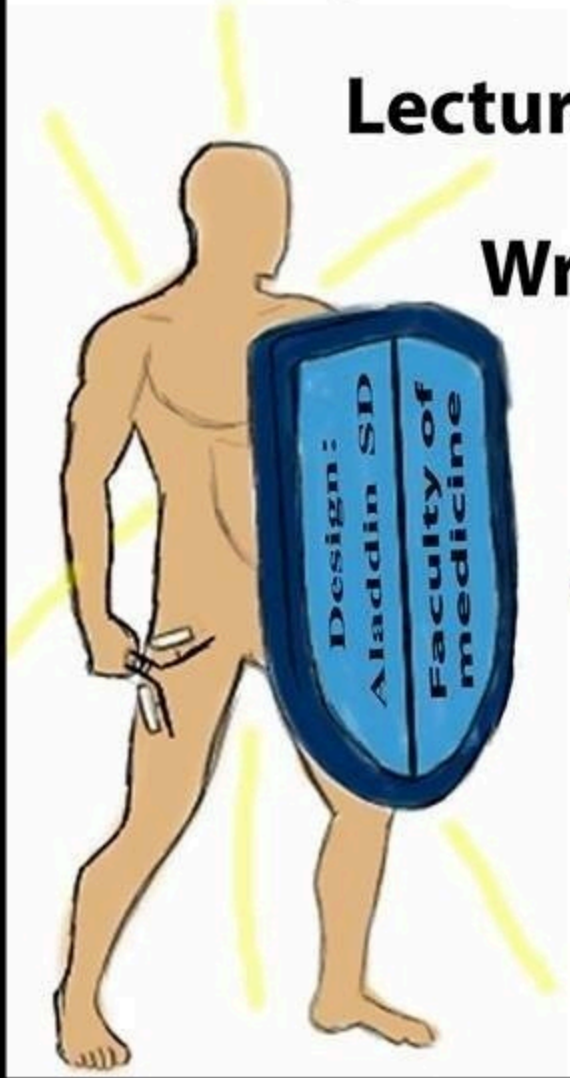
Medical Committee
The University of Jordan

# IMMUNOLOGY

**Lec#☐,Date( / /2014)**

**11+12**

**Subject:**

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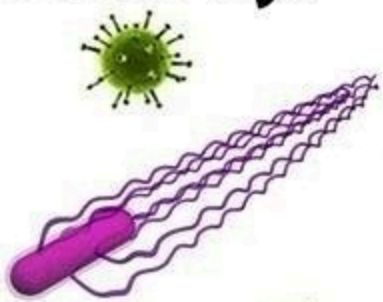
**Written by:**



**6/8/2014**

**Price:**

**10**

**Transplantation :**

Rejection differs from normal immune responses in two ways :
1)- They are stronger reactions.
2)- Two sets of APC's are involved, host and donor.

Types of grafts :
Autograft, allograft, syngenic and xenograft.

The antigens responsible for graft rejection are Two :
Major and minor HC antigens. Minor HC antigens are proteins (like foreign proteins).

Rejection of grafts is a big problem :
Hyperacute : presence of preformed antibodies, ABO incompatibility, anti HLA antibodies ( more serious ). Complement is involved resulting in lysis and thrombosis, this is more with xenografts as the complement regulator proteins are species different.
Kidney and heart are more susceptible to this rejection, while liver and skin are less. Probably size in case of liver.

Acute : antigen (donor MHC) presentation by host APC, or presentation by donor APC (known as passenger cells) transferred with the graft. The mechanism of rejection is probably through CD4 and CD8 cells. NK cells also, cytokines.
Humoral factors may be involved in accelerated rejection which occurs a few days after transplant, not so dramatic as hyperacute.

Chronic : Actual mechanism is not known, due to narrowing of blood vessels and eventual obliteration. Probably cytotoxic and DTH mechanisms are involved and humoral factors.
•Important observations made are; the presence of anti-donor antibody, refractoriness to increases in immunosuppression, and a high correlation between the onset of chronic rejection and history of early acute rejection episodes.

**•Donor-Recipient Matching**
**•MHC matching**
- Improves the success rate but does not prevent rejection.

- HLA typing is imprecise owing to the polymorphism and complexity of the human MHC.

- Grafts between HLA identical siblings are invariably rejected, albeit more slowly, unless donor and recipient are identical twins (minor H antigens).

The rejection is directed mainly at the graft MHC molecules and that is why it tends to be strong, 5% of all lymphocytes may be activated in one go.
Grafts of identical HLA siblings are eventually rejected because of the presence of minor histocompatability antigens which are probably self peptides bound to MHC I molecules.

First successful renal graft in 1954, advances in HLA testing, immuno-suppressing drugs, cyclosporin and monoclonal antibodies have improved the outcome.

Kidney tranplantation :
1)- ABO blood matching, antigens are present on endothelial cells as well as blood cells.
2)- HLA matching of haplotypes between related donors ( zero, one or two haplotype matching ).
3)- Recipients are screened for anti-HLA antibodies.
HLA cross-matching to detect antibodies in recipient against HLA antigens in donor, positive cross-matches are contraindicated. Antibodies are formed mainly through pregnancy and previously rejected grafts, and blood transfusions.

4)- Cadaveric transplants : ABO match, negative cross match for antibodies, best match for HLA ( A,B,C,DR and DQ ). Donor must be free from malignant or chronic disease and infection e.g. hepatitis viruses etc.
Cadaveric kidney is flushed and perfused with cold solution, or stored on ice, transplant within 48 hours is preferred.
Post operative suppression with azathioprine, prednisolone. Cyclosporin and monoclonal antibodies eg OKT3 against T cells.

Liver transplant :
ABO matching and liver size are important. The transplanted liver is resistant to hyperacute rejection (unknown cause), HLA typing is not performed, because it does not affect the outcome.

Pancreas transplant :
Whole pancreas or islet cells.
ABO and HLA matching is done. Positive cross-matches are not accepted.

Heart transplant :
Cross match for ABO. Screen for HLA antibodies.
Heart should be transplanted within 6 hours of harvesting.
Transplant within 4-6 hours.

Bone marrow transplant :
Best with identical twins (syngeneic), then with identical HLA donor (allogenic). Thus it is difficult to match.
Recipient marrow must be destroyed unless it is already non-existent (SCID).
Problem with GVH affecting liver, skin and intestine eventually leading to death of the patient. Even in HLA identical transplant, it may occur probably due to minor histocompatibility antigens.
Removal of mature T lymphocytes may be of benefit.

Foetus as graft :
Placental outer cells lack MHC molecules. Also the placenta probably secretes suppressive cytokines mainly a TH2 response. Oestrogen suppresses T cell activity, but promotes antibody synthesis.
HLA-G protects against attack by NK cells.

CORNEA

Immunodeficiency.

Many inherited immunodeficiencies are recessive, that is why many are X-linked.

Innate deficiency :

**1-Complement deficiency :**

Classical pathway : C2 deficiency is the commonest ( 1 in 20,000 ), deficiency has been found for C1q, C1r, C2, C4. These are not commonly associated with infection because of an intact alternative pathway. Immune complex disease e.g. SLE is common with early classical deficiency.
Deficiency of properdin, factor D and C3 are usually associated with repeated infections.
Deficiency of C5-C9 lead to susceptibility to Neisserial infections (organisms capable of intracellular survival).

Deficiency of other complement proteins :
C1 inhibitor : leads to angioneurotic oedema ( autosomal dominant ), the mediator is a split product of C2 called C2 kinin, or activation of the kinin system through Hageman factor.
85% of patients have a defective gene, the product of the other gene is not enough to control activation of C1.
15% have one gene mutation that produces non-functional C1 inhibitor protein.
Factor I and H : rare, leads to repeated infection because of excessive consumption of C3.
Deficiency of membrane protein regulators : DAF, HRF (C8bp), CD59 leads to PNH where there is increased lysis of RBC.
Deficiency of complement receptors : CR3 and CR4 (LAD) leads to repeated infections.
CR1 defeciency may lead to reduced I.C. clearance by RBCs

**2-Immunodeficieny associated with abnormal function of macrophages and neutrophils (phagocytic cell defects) :**

Chronic granulomatous disease :
Rare , 1 in one million population, autosomal recessive 2/3 are sex linked.
Onset within the first 2 years.
There is a deficiency of an enzyme (cytochrome oxidase) associated with oxygen burst and production of superoxide radicals in phagocytes especially neutrophils. There is repeated infection with granuloma formation of macrophages due to chronic bacterial infection. It is often fatal.
Diagnosis : NBT.

G6PD : similar to CGD but less severe. Defective generation of H2O2. Rare and not present in G6PD erythrocyte deficiency.
Abnormal NBT Nitroblue tetrazolium.

Myeloperoxidase deficiency : defective intracellular killing of bacteria by H2O2.

Leukocyte adhesion deficiency (LAD) :
Rare autosomal recessive, 100 cases reported to date.
Impaired β chain (CD18) leading to impaired production of LFA-1 (CD11a,CD18), Mac-1 or CR3 ( CD11b,CD18), p190,95 or CR4 ( CD11c,CD18) all of which are beta 2 integrins.
Adhesion to molecules on endothelia, chemotaxis, aggregation of neutrophils and phagocytosis are all impaired, leading to recurrent bacterial infections

Chediac-Higashi syndrome :
Rare, autosomal recessive. There is generalised cellular abnormalities leading to fusion of cytoplasmic granules affecting
macrophages and neutrophils leading to infections (failure to fuse lysosomes with phagosomes). Giant granular inclusion in cytoplasm.
melanocytes leading to albinism.
neurones leading to nerve defects.

Bone marrow graft may be curative.

Hyper IgE syndrome Job's syndrome;
Skin infections with Staph., high IgE.
An immunoregulatory T cell abnormality has been suggested as the cause with excessive IL-4 production.

**Primary defects of B cell and antibody production :**

I)- Bruton's agammaglobulinaemia : incidence 1 in 100,000.
Major immunological features :
- Recurrent pyogenic infections by 5-6 months of age.
- IgG less than 200 mg/dL, with absent IgM, IgA, IgD and IgE.
- B cells absent from peripheral blood.
- Good response to treatment with Ig replacement.

The deficient gene codes for Btk (Bruton's tyrosine kinase).
B cell maturation is halted at the pre-B-cell stage ( $\mu$ chain).
All other immune cells are normal.
X-linked (gene on long arm of chromosome X), low or undetectable Ig's in serum, reduced or absent B cells in serum, no germinal centres in lymphoid tissues, no plasma cells (in intestinal biopsy).
Pre- B cells in bone marrow are normal in numbers, thus there is a block in the maturation of pre-B cells into surface IgM expressing B cells. T-cells are normal.
Repeated infections. Appears at 5-6 months of age, differentiate from hypogammaglobulinaemia of infancy which may be prolonged for 18 months.
Reduced isohaemagglutinins. Failure to produce specific antibody after immunisation. Absent Ig after immunization. NB no live vaccine.
Treated with pooled gamma globulin injections, monthly IV. More during infections and antibiotics.
Prognosis : live into 20-30's.

Transient hypogammaglobulinaemia of infancy :
Appears at 5-6 months, IgG about 350 mg/dL, may last 18-24 months of age. B cells are present, normal levels of IgA and IgM.
B cells are present in blood.

2- IgA deficiency : common 1 in 700. Failure of differentiation of surface IgA expressing B cells into developing into plasma cells. Most patients are normal, some may have URTI. Some patients show a tendency to allergy, possibly that the absence of IgA in secretions allows the absorption of allergens across mucosal surfaces.
There is also an increased incidence of autoimmune disease.
Mechanism is unknown, a gene mapping to MHC class III region is suspected to be involved.

3- IgG deficiency : IgG2 and IgG3 are the commonest, associated with increased infection. IgG4 deficiency tends to be asymptomatic.

4- X-linked Hyper-IgM syndrome :
High levels of IgM associated with deficient IgA and IgG because heavy chain switching does not occur. Many of the IgM are auto antibodies.
The defect is lack of CD40 ligand on activated T cells, the B cells are normal but cannot differentiate in response to T-dependent antigens. Response to T-independent antigens is normal leading to increased IgM.

5- Common variable immunodeficiency :
- Recurrent pyogenic infections at any age (usually 15-35 years).
- Increased incidence of autoimmune disease.
- Total Ig less than 300 mg/dL. IgG less than 250.

- B cell numbers usually normal.

Defect in the terminal differentiation of B cells into plasma cells. There is no secretion of antibody.
Age of onset 15-30 years, males and females. B cells present but no plasma cells.
Isohaemagglutinins are either absent or very low.
Production of suppressor cells, lack of helper T cells and enzyme deficiencies have been blamed.

6- Good syndrome :
Acquired hypogamaglobulinaemia in adults with a thymoma. T cell immunity may be affected.

7)- Selective IgM deficiency : Normal IgG and IgA, this contradicts the theory of sequential Ig development.
Infection with polysaccharide containing bacteria. Autoimmune disease.

**Primary T-cell defects :**

1- DiGeorge syndrome (congenital thymic hypoplasia) :
- Aplasia of the thymus and parathyroid.
- Hypocalcaemia.
- T-cell deficiency.
- Ig levels and function normal..
- Facial abnormalities.
- Congenital heart disease.

Defective development of the thymus from the third and fourth pharyngeal pouches, there is parathyroid deficit, heart anomalies and abnormal facies.
T-cells are absent or greatly reduced in the blood. Antibody levels are variable. T-cell function occasionally improves with age and returns to normal by the age of 5, due to extrathymic tissues or thymic remnants.
90% of patients have a deletion in chromosome 22.
Early (under 14 weeks, to avoid GVH) foetal thymic transplant is effective.

2- Chronic mucocutaneous candidiasis :
Selective defect in T cell immunity to candida infection (intact T-cell immunity to most other antigens), antibody response even to candida is normal. There may be associated endocrinopathies e.g. hypoparathyroidism or Addison's disease. It has been suggested that it is basically an autoimmune disease affecting endocrine glands, the thymus being considered also as an endocrine gland.

**Combined immunodeficiencies :**

1)-Severe combined immunodeficiency SCID :
Onset in the first 3 months of life. Viral, bacterial, protozoal and fungal infections.
Lymphopenia < 1500 per cu.mm. T cells <200.
There are 2 types according to inheritance :
a) : autosomal recessive (Swiss type).
b) : X-linked recessive.50% of cases, ( T-B+NK- ) defect in the gene coding for gama chain of the IL-2 receptor.

About a third of SCID patients have a defect in genes coding for recombinase activity proteins RAG1 and RAG2.
T-B-NK+
There is depressed T and B cell immunity.

10% are due to autosomal recessive JAK-3 kinase : (T-B+NK-)

Early diagnosis is essential, as patients should not receive live viral vaccines (polio) or blood products containing competent lymphocytes (GVH).
Treatment by bone marrow Stem cell transplantation (compatible, or treated monoclonal antibodies to remove competent lymphocytes, to prevent GVH).

2)- Ataxia-telangiectasia :
Autosomal recessive, ? a genetic defect in DNA repair that results in a multitude of symptoms of this disease including neurological, vascuiar, endocrine and immune defects. It becomes worse with age.

3)- Wiskott-Aldrich syndrome :
Immunodeficiency, thrombocytopenia, eczema.
An abnormal protein ( WASP present on all haematopoeitic cells playing a role in signal transduction ) which results in abnormal development of B and T cells and platelets.
X-linked inheritance, bleeding due to thrombocytopenia (the platelets are smaller than normal), then recurrent infections and eczema.
Bone marrow transplant may be curative.

4)- Enzyme defeciency :
Varied degrees of B and T cell defeciency due to enzyme defeciencies, adenosine deaminase, nucleoside phosphorylase, this results in accumulation of metabolites that inhibit lymphocyte differentiation, leading to SCID.

5)- Genetic abnormalities of cytokine receptors result in SCID.

6)- Bare lymphocyte syndrome :
Class I, II or both may be deficient.
SCID picture.
Lacking MHC II molecules (lack of these in thymus results in absence of CD4 cells), autosomal recessive usually in consanguineous marriages.
MHC class I can be absent, lack of CD8 cells.