Immunity: protection from infectious pathogens including host reactions against cancers, tissue transplant & self antigens.

Innate	Adaptive / Acquired
→ 1st line of defence	→ 2nd line of defence
→ always present since birth	→ developed during lifetime by experience (activated only on exposure to antigen)
→ no lag phase (immediate action)	→ Lag time of response
→ Receptors of innate immunity recognize broad molecular patterns shared by several pathogens ⇒ PAMP's [pathogen associated molecular patterns]. eg: – TLR-4 receptor recognizes LPS of gram -ve bacteria – flagellin – ss RNA.	→ Receptors recognize organism specific antigens • T cell receptors (TCR) • B cell receptors (BCR)
• These receptors aka Pattern Recognition Receptors (PRR's)	→ narrow specificity & unlimited diversity.
→ PRR's have a broad specificity but limited diversity	→ genes for these receptors are generated by somatic recombination in primary lymphoid organs.
→ PRR are encoded in germ-line DNA.	
→ No memory.	→ memory present.

Components of Innate Immunity:

① Anatomical & physiological barriers

(a) skin with acidic pH (due to lactic acid & other fatty acids in sebum)

(b) mucous membranes

(c) Acidic pH of stomach

(d) Antimicrobial peptides in blood & mucous secretions

eg: α, β - defensins, hepcidins, cathecidines

(e) Lysozyme & other hydrolytic enzymes in tears, saliva & mucous secretions

(f) Commensal Flora - provide colonisation resistance

② Monocytes, tissue macrophages
→ marker: CD 14

③ Neutrophils, eosinophils, basophils
→ marker: CD 66b

④ NK cells (marker ⇒ CD 16, CD 56)

⑤ Mast cells

⑥ Dendritic cells

⑦ NKT cells

⑧ γδ T-cells.

⑨ Complement System: 11 complement proteins + several regulatory proteins

- C1q, C1r, C1s ⇒ C1 complex ($C1q_2r_2s_2$)
- C2 - C9

Most abundant complement protein: C3.

→ generally synthesized in liver

Immunity:

Innate

→ present by birth

→ non-specific

→ no memory

- Epithelial Barriers – Skin – GIT
- Plasma proteins – CRP
- Cells – Neutrophils – Macrophages – Dendritic cells – Complements
- Pattern Recognition Receptors

Acquired / Adaptive

→ developed later on exposure to antigens during lifetime

→ specific

→ memory present

- B-lymphocyte (humoral) → produce Ab.
- T-lymphocyte (cell-body)

Pattern Recognition Receptors [PRR]: present on plasma membrane / cytoplasm / endosome

↳ recognize specific patterns on surface of microbes

→ If present on plasma membrane: it detects extracellular organisms

If present in cytoplasm: it detects intracellular organisms

If present on endosome: it detects the ingested microbes

PRR

Toll-like receptor (TLR)	C-Lectin Receptor [CLR]	Rig-like Receptor (RLR)	Nod-like Receptor (NLR)
→ 10 TLRs have been identified → located on plasma membrane & endosomes → detect gram +ve & gram -ve bacteria	→ located on plasma membrane → detect fungal glycans	→ present in cytoplasm → detect viruses → stimulate the production of antiviral cytokines	→ present in cytoplasm → detects • N - necrotic debris • O - Ion transport • D - diabetes mellitus

NOD-like Receptor:

presence of N/O/D

↓

activation of caspase 1

↓

production of IL-1

↓

inflammation (fever)

[∵ inflammasome can be involved with NLR]

Natural killer (NK) Cell: they can kill cells without prior sensitization

→ usually produced by a large granular lymphocyte.

→ constitutes 5-10% of circulating blood lymphocytes.

→ Not a B-cell or a T-cell } ∴ called NULL CELL
No B-cell or T-cell receptors }

→ Not MHC restricted

Function:

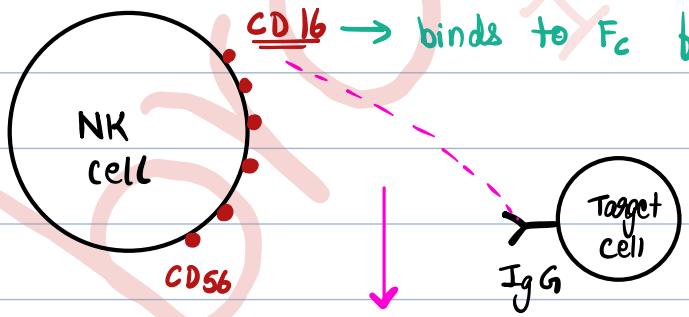
Innate

→ it can directly kill the virus infected cell or tumor cells.

Adaptive

→ it can lead to Ab dependent cell-mediated cytotoxicity [ADCC].

Markers for NK Cell:
- CD 16
- CD 56 (role is still not understood)



Killing of target cell (by releasing toxins & perforins which leads to release of granzyme)

NK Cell

has

Activating Receptors

- NKG2D

Inhibitory Receptors

- CD 94
- CD 96.

prevent killing of self cells by NK cells

Cytokines Produced By NK Cell:

↓

IFN-γ

↓

activation of macrophages to form epithelioid cells

Cytokines Responsible For Proliferation of NK cells:

- IL-2
- IL-15.

Dendritic Cells (DC): cells with numerous fine cytoplasmic process resembling dendrites ; important APCs

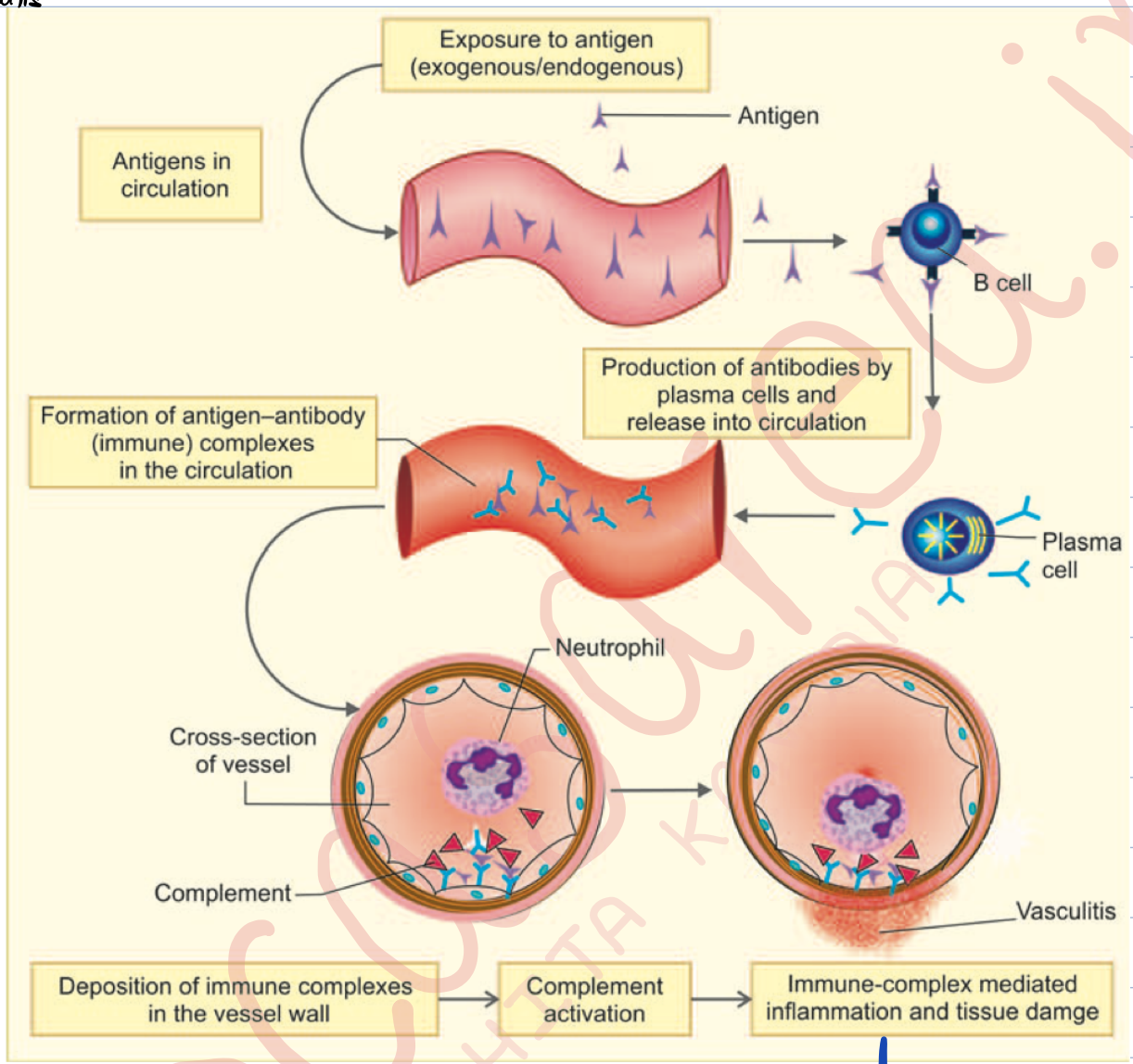
Types

IDC (Interdigitating): most imp. APCs for initiating T-cell responses
↳ below epithelial lining, interstitia of all tissues
→ Immature IDC with epidermis = Langerhans cell

Foliculas DC: in germinal centres of lymphoid follicles in spleen & lymph nodes
↳ act as reservoir for HIV in AIDS

Arthus Reaction (Local Immune Complex Disease):

→ local area of tissue necrosis usually in the skin, resulting from acute immune complex vasculitis



↓

fibrinoid necrosis & thrombosis

↓

Ischaemic injury

B-Lymphocyte:

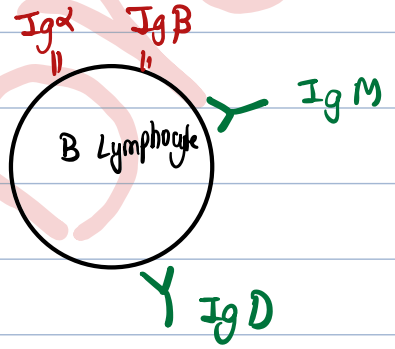
→ constitute 15-20% of circulating blood lymphocytes
→ provide humoral immunity (against extracellular microbes)
→ lymphocyte matures in the bone marrow

Sites of B-lymphocytes:
- cortex of lymph node
- Peyer's patches in GIT
- White pulp of spleen.

Markers:
- CD 10 / CALLA (Common ALL antigen)
- CD 19, 20, 21, 22, 23
- Ig α (CD 79a)
- Ig β (CD 79b)

- **Pan B-cell marker:** CD19
- **Receptor for EBV on B cells:** CD 21.

B Cell Receptor: IgM or IgD Ab



Mechanism of Activation of B - Lymphocytes :

T-cell independent pathway

→ activated if the antigen is a LPS [lipopolysaccharide]

↓

Activates B - lymphocyte

↓

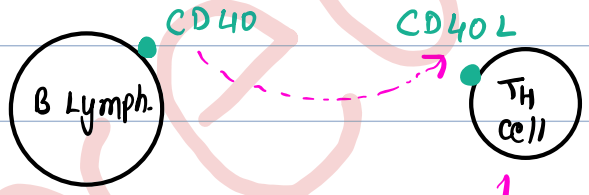
formation of plasma cells

↓

production of IgM

T-cell dependent pathway

→ activated when the antigen is a protein



↓

IgM , IgD

- IL-4
- IFN-γ

IgG IgA IgE

[formation by class switching]

IgM ⇒ Millionaire's Ab ⇒ due to highest molecular weight of its pentameric structure.

T-lymphocyte:

→ responsible for cell-mediated (intracellular) immunity

→ constitute 60-70% of circulating blood lymphocytes.

→ CD4 : CD8 = 2:1

- decreased in: HIV
- Increased in: Sarcoidosis

→ T-lymphocytes mature in the thymus

Sites of T-lymphocytes:
- paracortex of lymph nodes
- PAL [peri-arteriolar sheets of spleen]
- intraepithelial lymphocytes.

Markers: - CD 1, 2, (3), 4, 5, 7, 8

↓

Pan T-cell marker

T-Cell Receptors:

↓

αβ

→ present in 95% cells

→ polypeptide

→ MHC restricted

↓

γδ

→ present in 5% T-cells

→ provides protection against those microbes that try to enter through the epithelial barriers

Types of T-cells:

Helper T cell (T_H)

→ called CD4+ T-cell

→ MHC II restricted

→ first line of defense in the body

Functions:

- helps the B-cells to produce Ab's
- activation of macrophages

Cytotoxic T-cell [T_C]

→ called CD 8+ T-cell

→ MHC I restricted

→ 2nd line of defence

Functions:

- directly kills the cell by peaforin - granzyme mechanism.

Types of T_H Cells:

T_H 1

→ Cytokines produced:
- IFN-γ
- IL-12

→ helps in activation of macrophages

→ helps in production of IgG Ab.

→ helps in fight against intracellular microbes

T_H 2

- IL-4 → increases production of IgE → activation of macrophages
- IL-5 → helps in production of eosinophils → activation of mast cells.
- IL-13 → activation of macrophages

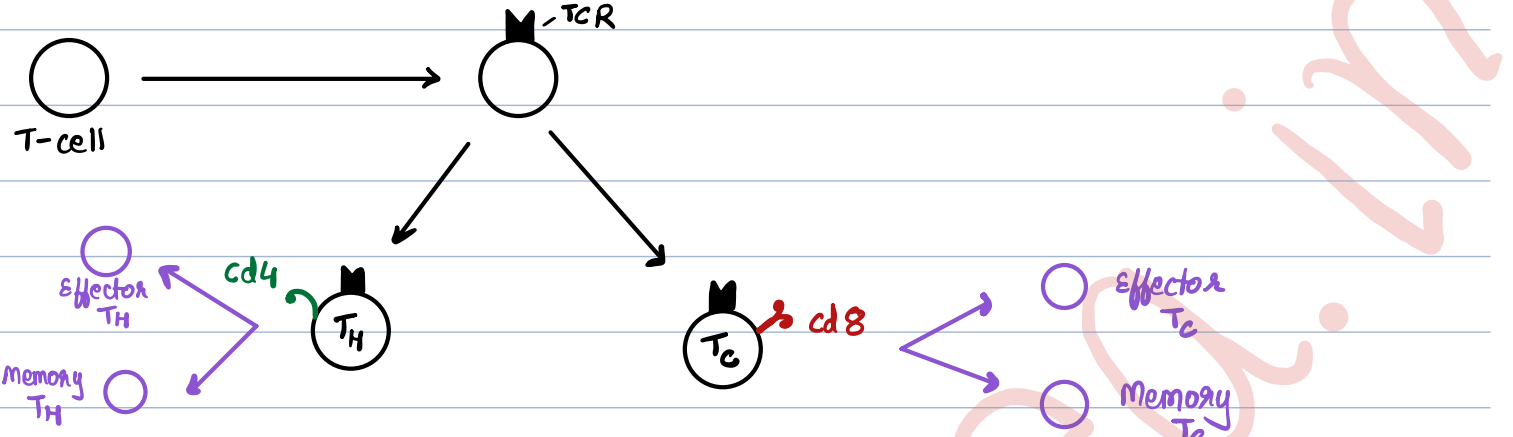
help in fighting helminthic infections

T_H 17

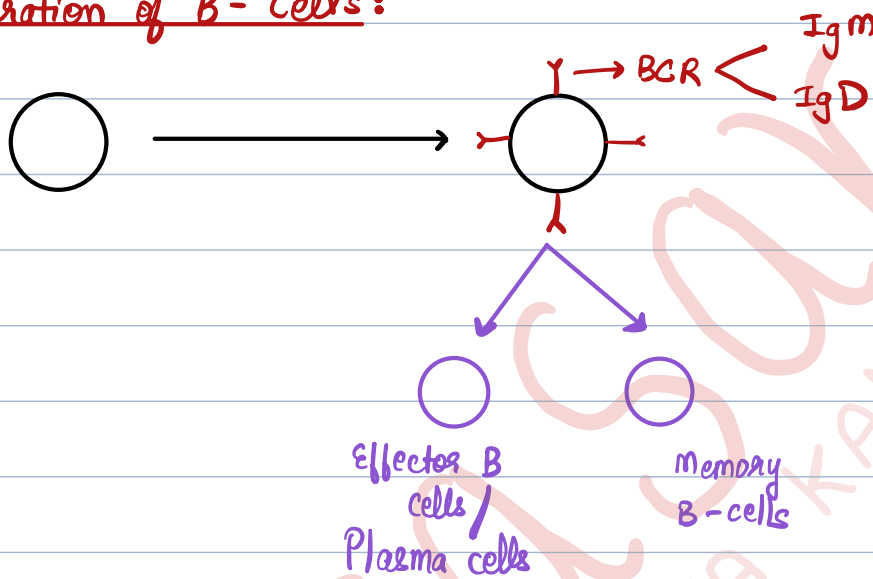
- IL-17
- IL-22

role in recruitment of neutrophils & macrophages → helps in fight against extracellular microbes.

Maturation of T-cell:

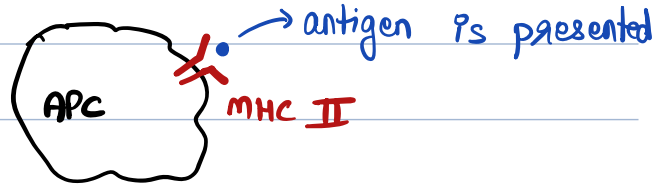


Maturation of B-cells:

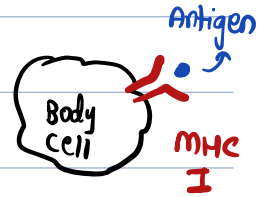


Extracellular antigen → MHC II + antigen phagocytosed by APC

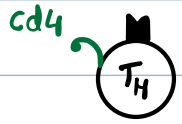
↓



Intracellular antigen → MHC I + Body cell →

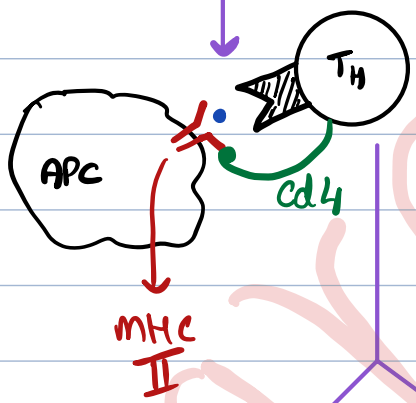


CMI:



TCR recognizes the Ag fragment presented by MHC II on the surface of cd4

co-stimulation by IL-2



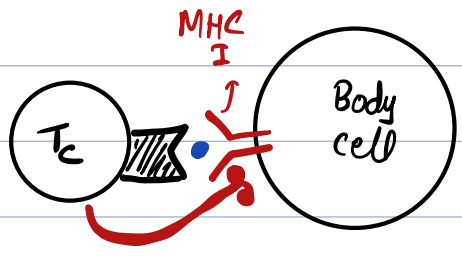
Effector T_H | Memory T_H

TCR recognizes Ag fragment displayed by MHC I on surfaces of:

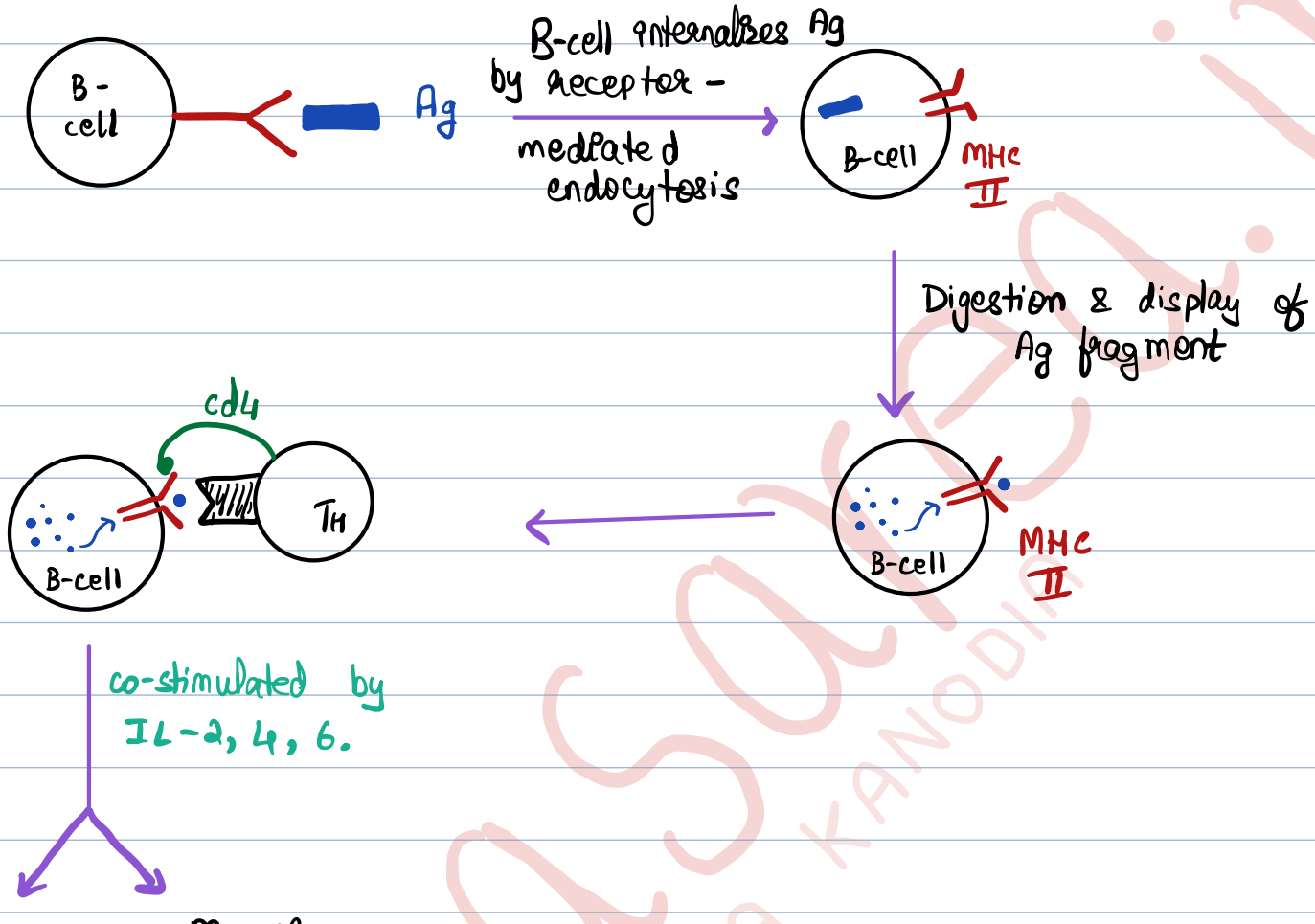
- any body cell
- cancer cell
- tissue transplant

co-stimulation by IL-2

Effector Tc | Memory Tc



AMI:



Hypersensitivity Reactions (HS Rx):

I, II, III } Ab mediated

IV ⇒ cell mediated

V ⇒ modification of Type II

→ exaggerated immune response

→ pre-sensitized (immune) state

→ injurious consequences in the sensitized host, following subsequent contact

TYPE	DESCRIPTIVE Name	INITIATION Time	MECHANISM	EXAMPLES
I	IgE-mediated hypersensitivity	2-30 mins	Ag induces cross-linking of IgE bound to mast cells with release of vasoactive mediators	Systemic anaphylaxis, Local anaphylaxis, Hay fever, Asthma, Eczema
II	Antibody-mediated cytotoxic hypersensitivity	5-8 hrs	Ab directed against cell-surface antigens mediates cell destruction via ADCC or complement	Blood transfusion reactions, Haemolytic disease of the newborn, Autoimmune Haemolytic anaemia
III	Immune-complex mediated hypersensitivity	2-8 hrs	Ag-Ab complexes deposited at various sites induces mast cell degranulation via FcgammaRIII, PMN degranulation damages tissue	Arthus reaction (Localised); Systemic reactions disseminated rash, arthritis, glomerulonephritis
IV	Cell-mediated hypersensitivity	24-72 hrs	Memory TH1 cells release cytokines that recruit and activate macrophages	Contact dermatitis, Tubercular lesions

Type I HS Rx: Anaphylactic HS

→ exogenous antigen

Examples:
- Any kind of atopy / allergy / anaphylaxis
- Bronchial asthma
- Casoni's Test → done for hyatid disease
- Drug reaction
- Hay fever
- PK reaction [Prausnitz – Kustner Rx]
- Theobald Smith phenomenon

[Atopy: naturally occurring familial HS]

Primary mediators	
Molecule	Effects
Histamine	Vascular permeability, SM contraction
Serotonin	vascular permeability, SM contraction
ECF-AS	Eosinophil chaemotaxis
NCF-A	Neutrophil chaemotaxis
Proteases	Mucus secretion, connective tissue degradation

Secondary mediators	
Molecule	Effects
Leukotrienes	Vascular permeability, SM contraction
Prostaglandins	vasodilatation, SM contraction, platelet activation
Bradykinin	vascular permeability, SM contraction
Cytokines	numerous effects inc. activation of vascular endothelium, eosinophil recruitment and activation

PK reaction: serum from an allergic person is injected intradermally into a non-allergic individual. Later, when the apt. allergen is injected at the same time, a wheal & flare reaction is developed at the site.

Mechanism:

Ag (ex: pollen) + APC

↓

presentation of Ag to T cell

↓

Activation of T_H2 cell

↓

IL-4 → increased synthesis of IgE

IL-5 → increased synthesis of eosinophils

IL-17 → increased mucous production

IgE → FcεRI receptor → MAST CELL

on repeat exposure → MAST CELL

(cross-linking) Polymerization of IgE on mast cell → *

* mast cell activation
↓
release of mediators
↓
HS Rx

Preformed (present in the granules of mast cell)
① Histamine ② Proteases
③ Chemotactic factors

Phospholipase A2 gets activated
↓
- production of arachidonic acid metabolites (prostaglandins, leukotrienes)
- synthesis of platelet activating factor (PAF)

Phases of Type I HS Rx:

Immediate Phase
→ occurs in minutes

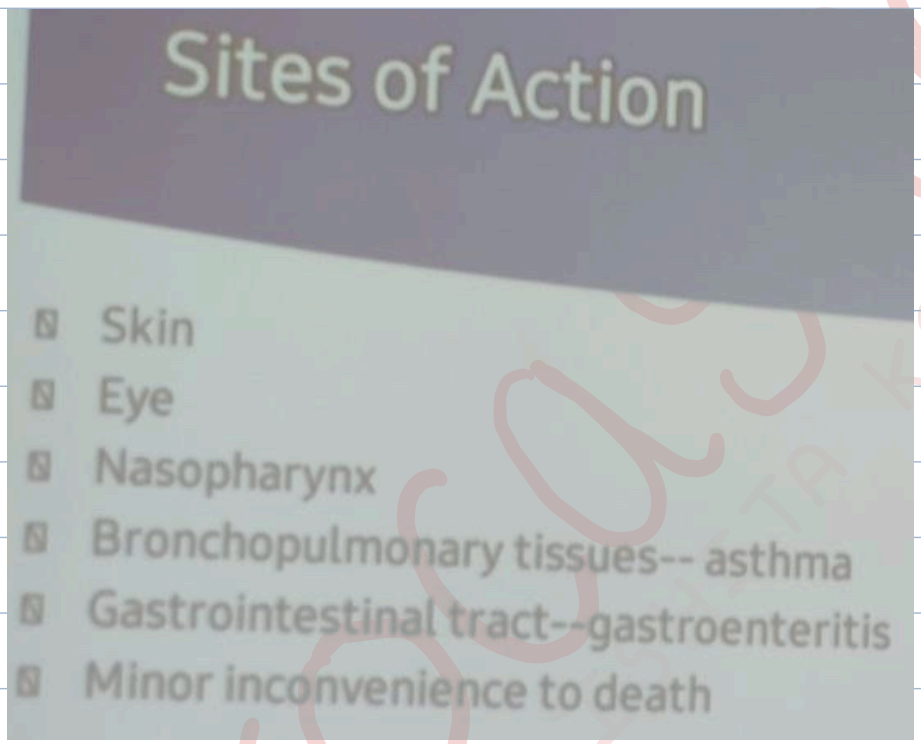
Changes:
- vasodilation
- increased vascular permeability
- increased mucous production

Late Phase
→ occurs in 2-24 hrs

Changes:
- fibrosis
- deposition of inflammatory cells
- epithelial damage

- Most imp. cell: Mast cell
  (Stain for mast cell : Toluidine blue)

- Imp. cell in late phase: Eosinophils
- Most imp. Ab: IgE
- most imp. cytokine: IL-4, IL-5
- Easliest mediator released: Histamine



Type II HS Rx: (Antibody-mediated Cytotoxic)

(endogenous Ag) → occuring on cell surface

Examples:

- My – Myasthenia gravis
- Blood – Blood transfusion Rx
- Group – Grave's disease, Good Pasteur Syndrome, Granulocytopenia
- Is – ITP, Immune hemolytic anemia
- R – Rheumatic fever
- H – Hyperacute graft Rejection
- Positive – Pernicious Anemia, Pemphigus vulgaris

Mechanism:

- Opsonization & Phagocytosis
- Inflammation & complement Activation
- Antibody dependent cell-mediated cytotoxicity [ADCC].

Opsonization & Phagocytosis: occurs when IgG is produced.

[IgG ⇒ one of the most potent opsonins]

IgG + cell

↓

cell becomes very tasty for macrophages due to IgG opsonin

↓

Macrophage will eat the cell

↓

HS Rx

Associated disorders:

- hemolytic disease of new born
- blood transfusion reaction
- Drug reaction.

Inflammation & Complement Activation:

→ occurs when Ab is bound to ECM or basement membrane

Ab
↓
Complement activation
↓
Neutrophil chemotaxis
↓
Tissue injury

- Good Pasteur Syndrome
- Glomerulonephritis
- Graft rejection

ADCC: no complement activation or tissue injury

→ Ab are produced against cell surface receptors

- Grave's disease: Anti TSH receptor Ab
- Myasthenia gravis: Ab against Ach receptor

Recently been classified as Type V Hs Rx.

↗ occurs in circulation. (exogenous / endogenous Ag)

Type III HS Rx : Immune complex Mediated

Examples : S – Serum sickness, Shick Test, SLE
- visceral lesions – type III
- hematological lesions – type II

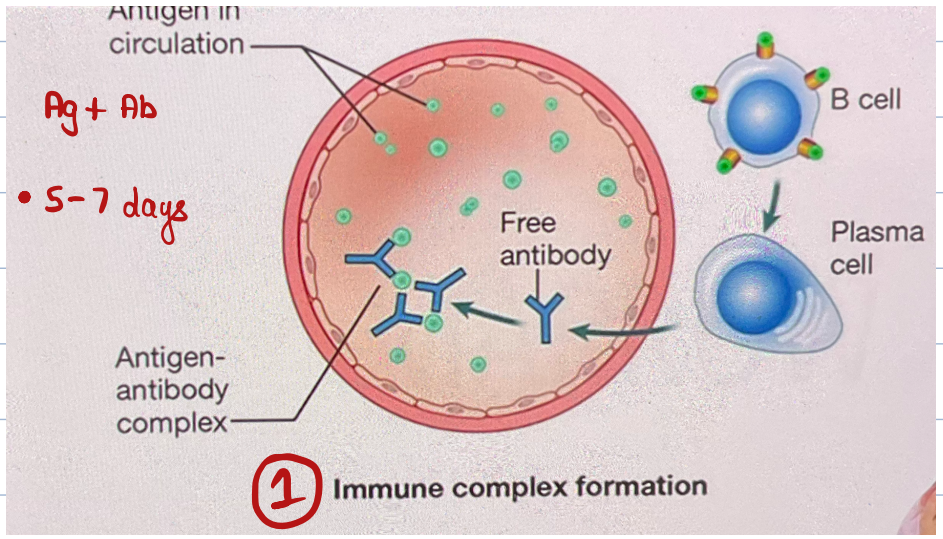
H – Henoch Schonlein Purpura

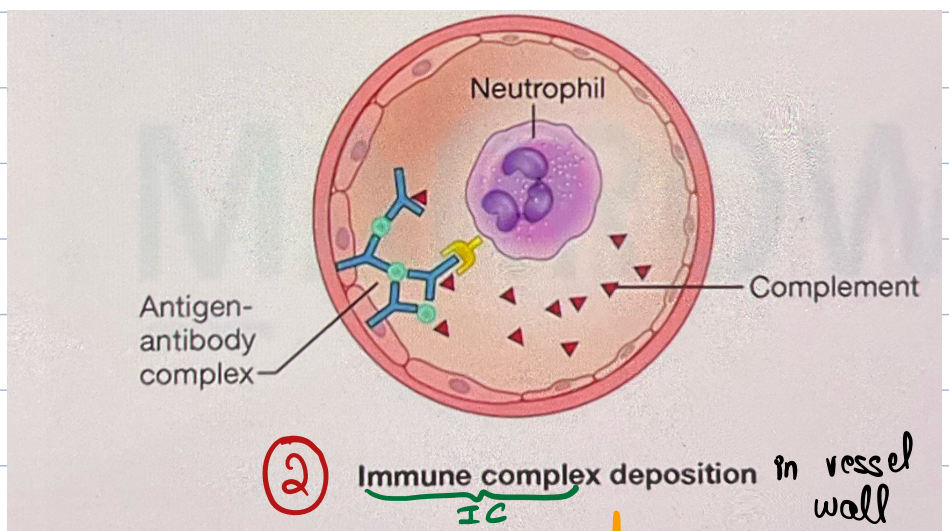
A – Arthus's Rx

R – Reactive arthritis

P – Post-streptococcus Glomerulo nephritis [PSGN]
- Poly-arteritis Nodosa [PAN]
- Membranous nephropathy.

Mechanism : [may take about 10-14 days for the whole process]





↓

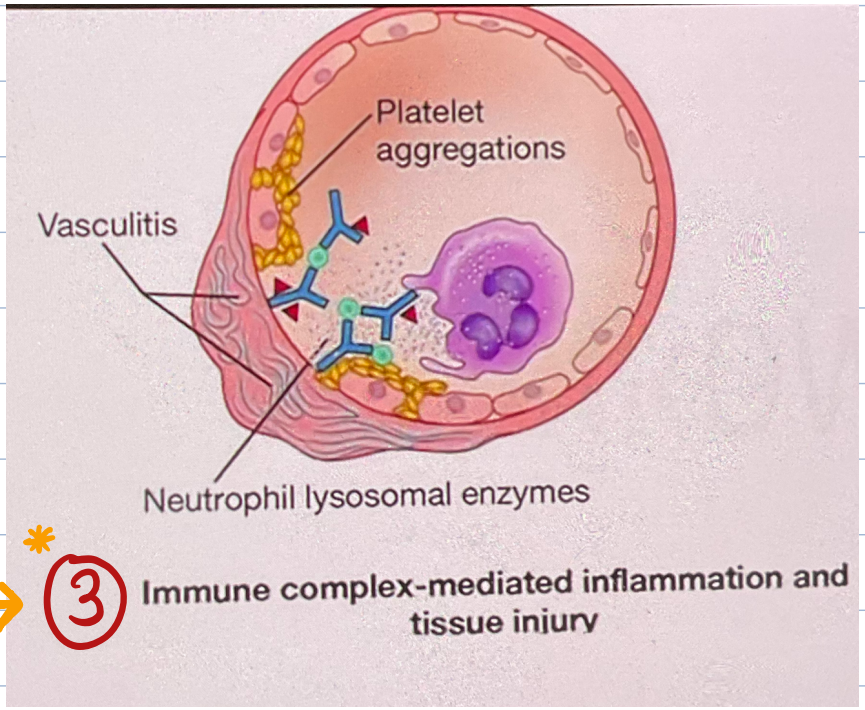
Complement activation → *

most pathogenic ICs :

→ small to medium sized

→ usually have Ag excess.

• IC are generally deposited in those organs that have a high filtration rate (eg: kidney, joints)



* ③ Immune complex-mediated inflammation and tissue injury

↳ mediated by interaction of TH1 CD4+ & Tc CD8+

Type IV Hs Rx: Cell-mediated Hs / Delayed Type Hs

Examples:
- granuloma formation
- tuberculin test
- lepromin test
- contact dermatitis
- Sarcoidosis
- Multiple sclerosis
- Rheumatoid arthritis (both Type IV & Type III)
- Hypersensitivity pneumonitis (both Type IV & Type III)
- Acute & chronic graft rejection

MHC : [major Histocompatibility complex]

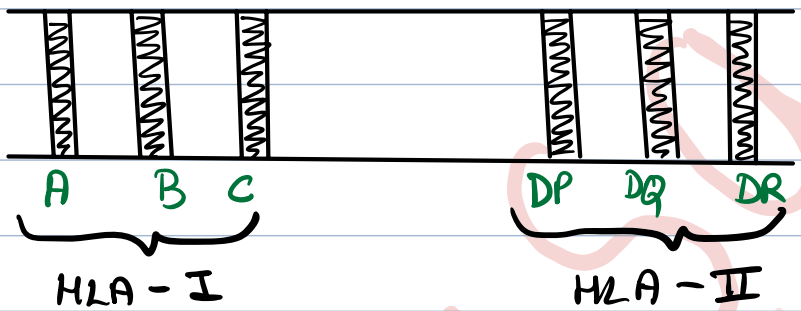
aka HLA [human leucocyte antigen]

→ gene on short arm of chromosome 6 (6p)

Function: small peptide molecules that present the antigen to antigen-specific T-cells.

Class I

Gene Loci:



Class II

Class III

→ recently discovered

→ encoded by heat shock proteins, complement proteins, properdin

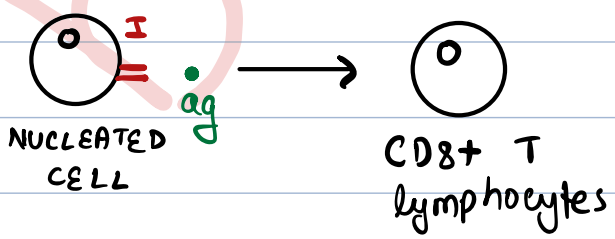
→ role in auto-immune disorders

HLA I

① Present on all nucleated cells + Platelets

② Gene loci - A, B, C

③ Presents Ag to CD8+ T lympho.



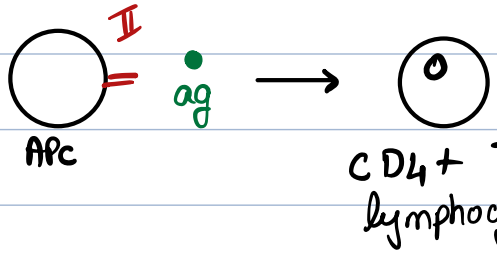
④ major role in graft rejection

HLA II

① Present only on APCs - B cells, fibroblasts, dendritic cells.

② Gene loci - DP, DQ, DR

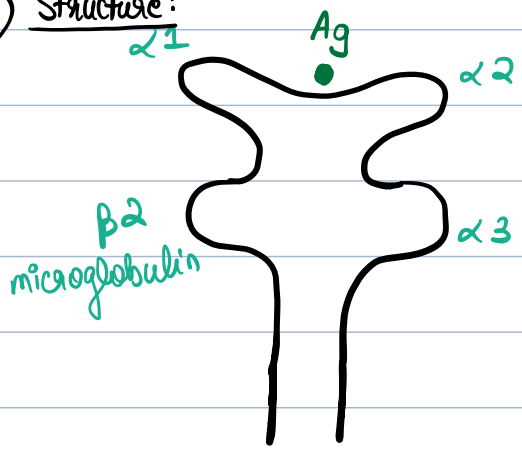
③ Presents Ag CD4+ T lympho.



④ major role in graft vs host disease [GVHD]

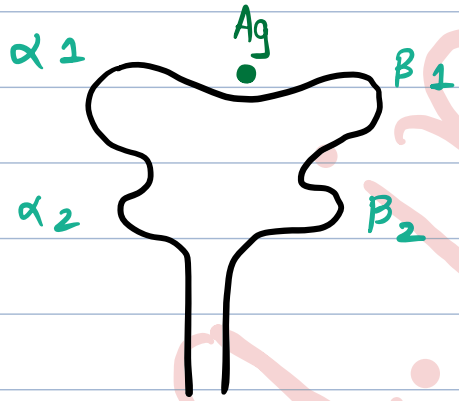
HLA I

⑤ Structure:



HLA II

⑤



Role of MHC:

→ can be used for paternity testing

→ for predicting the incidence autoimmune disorders

- HLA - B27 ⇒ Ankylosing Spondylitis
- HLA DR3, DR4 ⇒ Diabetes Mellitus
- HLA DQ2, DQ8 ⇒ Celiac disease
- HLA B5, B51 ⇒ Bechet's disease

→ anthropological testing

→ Organ transplantation – HLA matching

HLA Matching: (Typing)

I	II
A	DP
B	DQ
C	DR – most important HLA which needs to be typed

→ All 6 loci will match in 2 individuals only in identical twins

→ A, B, DR ⇒ must match for transplantation (DR > B > A)

→ every loci has 2 alleles

∴ for matching, score required = 6/6.

[HLA alleles are co-dominant]

HLA matching is not done for:

- cornea
- liver
- heart
- lung

} HLA matching not mandatory

Grafts:

- Isograft → between identical twins
- autograft → same body
- allograft → different individuals but same species
- xenograft → different species

- Orthotopic: → same anatomical location as the donor
- Heterotopic: → different anatomical location

Graft Reaction:

Graft Rejection

→ host is immunocompetent & host cells attack the graft.

- Rate of allograft rejection varies according to:
  - tissue involved
  - genetic distance b/w donor & recipient
  - immunological memory.

GVHD

→ host is immunosupressed & graft attacks host cells.

- seen in bone marrow transplantation (BMT) commonly.

→ occurs due to presence of a large number of lymphocytes in donor organ.

Vital grafts: live grafts (kidney, heart, etc.) expected to survive & perform physiological functions in the recipient.

Static grafts: Non-living structures (bone, artery, etc.) which merely provide a scaffolding on which new tissue is laid in the recipient.

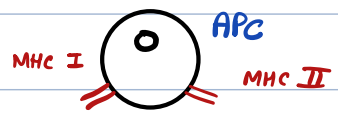
Graft Rejection:

Eg: kidney transplant

Mechanism:

Direct Pathway

→ Donor APCs start attacking the host immune system.



- destroy kidney tubules
- " endothelium

activation of IFN-γ

production of cytokines

Indirect Pathway

→ host APCs trigger the immune response

activation of IFN-γ

production of cytokines

- destroy kidney tubules
- " endothelium

Activation of B cells

production of Ig's

- Directly damage to tubules
- Complement activation

Types of Graft Rejection: ← hyperacute, acute, chronic

Hyperacute Graft Rejection:

→ occurs within minutes of transplantation [in less than 48 hrs]

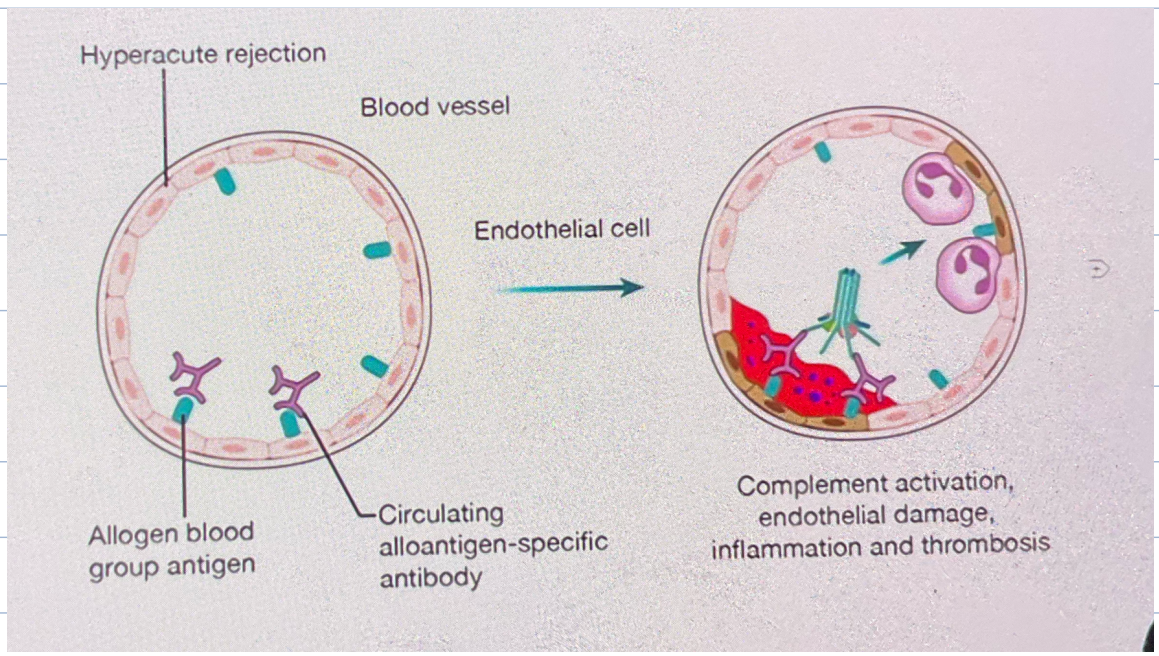
→ occurs due to preformed antibodies

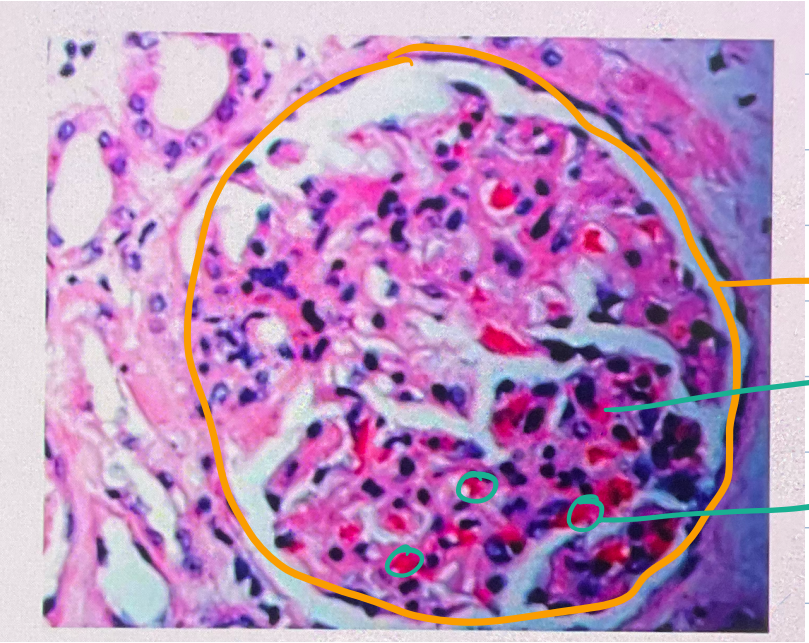
Type II HS Rx.

→ Preformed antibodies seen due to
- previous pregnancy
- ABO & RH incompatibility
- previous blood transfusion
- previous transplantation

GROSSLY: cyanosed, mottled, flaccid (kidney)

MICROSCOPICALLY:
- endothelial damage
- fibrinoid necrosis
- microthrombi
- Neutrophilic infiltrate





PREVENTION: Donor specific Ab Test must be done.

Acute Graft Rejection:

Acute cellular Rejection

→ mediated by CD4+ T cells or CD8+ T cells

Type IV HS Rx.

→ responsive to increasing dose of immunosuppressive drugs.

Microscopically:

TUBULO-INTERSTITIAL PATTERN

- tubulitis
- mononuclear inflammatory infiltrate

VASCULAR PATTERN

- endothelitis

Acute Humoral Rejection

→ mediated by Ab (newly synthesized)

→ Ab — endothelial damage
— complement activation

Type II or III HS Rx.

→ does not respond to immunosupressants

→ Tx: B-cell depleting agents.

Microscopically:

→ fibrinoid necrosis

→ peritubular capillaries show deposition of complement breakdown products: C4d

marker for acute humoral rejection.

Chronic Graft Rejection:

→ most common type

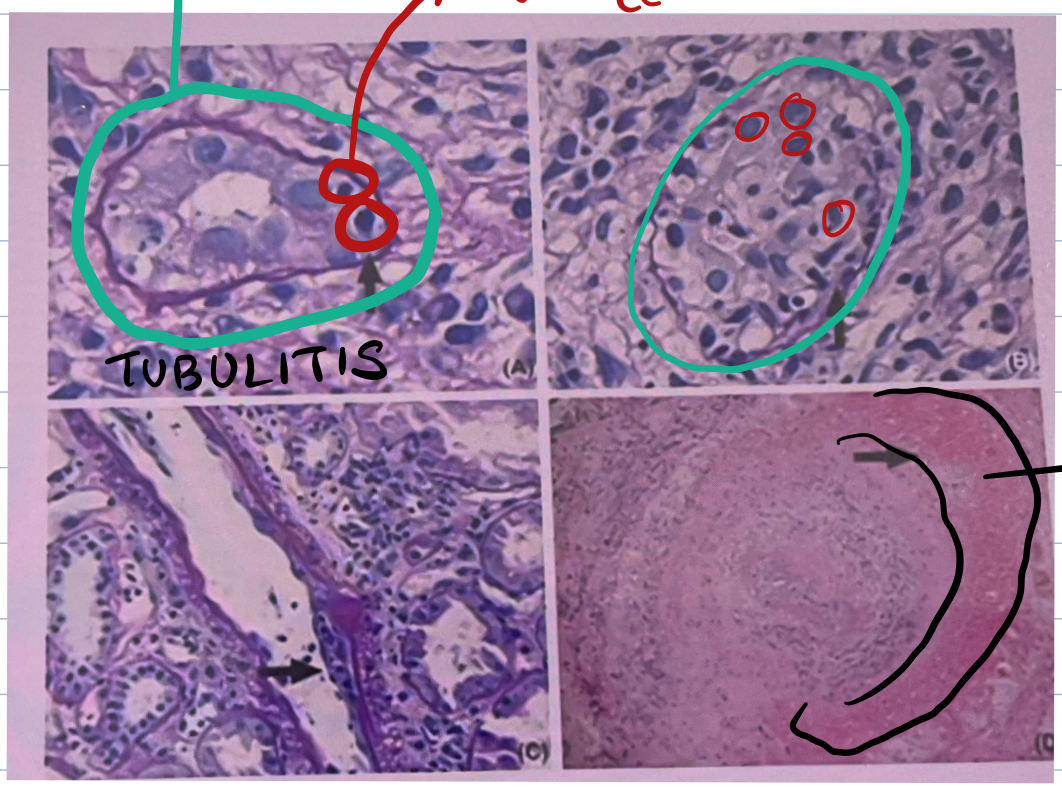
→ occurs in months - years

→ can be - cell mediated - Type IV HS

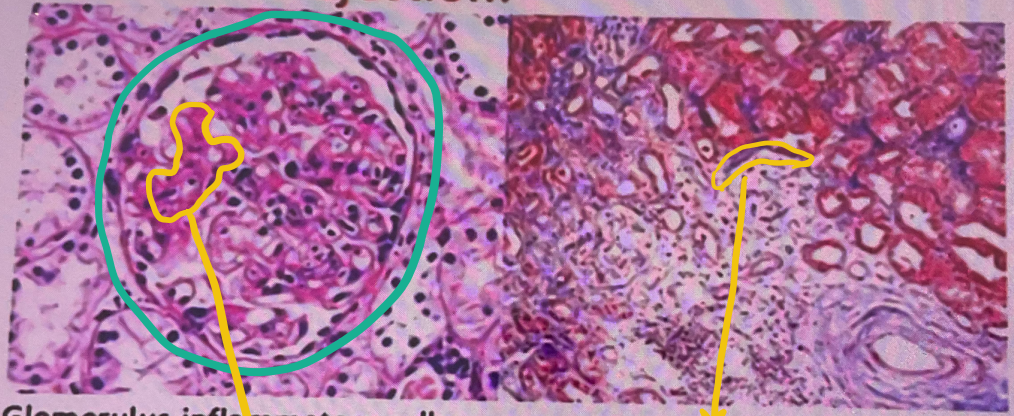
- Ab mediated - Type II HS

Microscopically:

→ Transplant glomerulopathy [duplication of glomerular basement membrane, interstitial fibrosis ; glomerulosclerosis ; tubular atrophy].



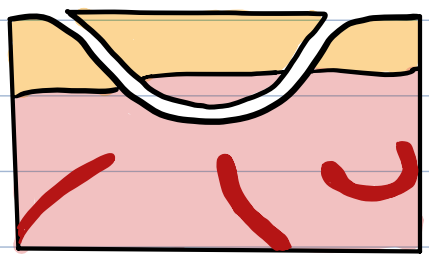
Chronic rejection:



Glomerulus-inflammatory cells within the capillary loops (glomeruliitis), accumulation of mesangial matrix, and duplication of the capillary basement membrane.

Interstitial fibrosis and tubular atrophy. (trichrome stain), contrasted with the normal kidney.

Artery-prominent arteriosclerosis



GVHD: complication of bone marrow transplantation (BMT) or hemopoietic stem cell transplantation

a.ka. Runt's disease (in mice)

→ Type IV HS Rx

Acute GVHD

→ duration < 100 days

→ Affected organs:

- skin ⇒ peeling / excoriation
- GIT ⇒ mucosal ulceration ⇒ diarrhoea
- Liver ⇒ jaundice.

Chronic GVHD

→ > 100 days

- skin ⇒ scleroderma
- GIT ⇒ strictures
- Liver ⇒ cirrhosis.

Conditions required for GVH reaction to occur:

- Graft cells must contain immunocompetent T cells
- Recipient should possess transplantation antigens that are absent in the graft
- Recipient may be immunologically suppressed & thus, cannot mount immune response against the graft.

Y-Linked Graft Rejection / Epchwald Slimser Effect:
(Sex linked)

→ occurs when a male gives a graft to a female (not vice versa)

male: XY → has a gene 'UTY'

↓

encodes for histone demethylase (aka. minor HC)

↓

considered as a foreign substance & graft rejected

female: XX

Complications of Grafts/Transplants:

① Infections:
- cytomegalovirus infection (CMV) ⇓ Owl's eye inclusions
- BK Polyoma virus ⇓ decoy cells

② Graft Rejection

③ GVHD

④ Increased risk of malignancies,
- SCC (HPV associated)
- Kaposi sarcoma [HHV-8 associated]
- Non-Hodgik's Lymphoma (NHL) [EBV associated]

⑤ Post-transplant lymphoproliferative disorder ↑.

Clinical Immunosuppression:

→ Succesful transplant: balance between recipient's immune response, donor's allograft & pharmacologic immunosuppression.

→ Immunosuppressant protocol:
- induction
- maintenance.

Complications: - increased incidence of opportunistic infections & malignancies
- Early infections: bacterial, viral, fungal
- Late infections: CMV, EBV, HSV
- Malignancies: Squamous cell carcinoma (most common)

Viral Malignancies:

• HPV	Ca Cervix
• HBV, HCV	HCC
• HHV 8	Kaposi's sarcoma
• EBV	PTLD

Immunosupressants:

Drug	Mechanism of Action	Adverse effects
Cyclosporine (CsA)	• binds to cyclophilin • inhibits calcineurin & IL-2 Synthesis	• Nephrotoxicity • Tremor • Hirsutism • Hypertension
Tacrolimus (FK506)	• Binds to FKBP • inhibits calcineurin & IL-2 Synthesis	• Nephrotoxicity • Neurotoxicity • Hypertension • GI Toxicity (nausea, diarrhea)
Mycophenolate mofetil	• Antimetabolite • Inhibits enzyme necessary for de novo purine synthesis	• Leukopenia • GI toxicity
sirolimus	• Inhibits lymphocyte effects driven by IL-2 receptor	• Thrombocytopenia • Poor wound healing • Increased serum cholesterol/LDL
Corticosteroids	• Multiple actions • Anti-inflammatory • Inhibits lymphokine production	• Cushingoid state • Glucose intolerance • osteoporosis
Azathioprine	• Antimetabolite • Interferes with DNA, RNA synthesis	• Thrombocytopenia • Neutropenia • Liver dysfunction
Belatacept	• T cell blocker	• Increased risk of bacterial infection

Immunodeficiency Disorders:

PRIMARY

Defect in Innate Immunity

~ see inflammation ~

Defect in Adaptive immunity

Defect in Lymphocyte Maturation

- Bruton's agammaglobulinemia (BTK, X-R)
- Digeorge syndrome (DeL 22q.11, T-cell)
- SCID
  - AR
  - XR

Defect in Lymphocyte Activation / Function

- Hyper Ig M syndrome (XR (mostly))
- CVID
- Isolated IgA def.

Systemic Disease / Syndromes

- Wiscott Aldrich Syndrome
- Ataxia telangiactasia

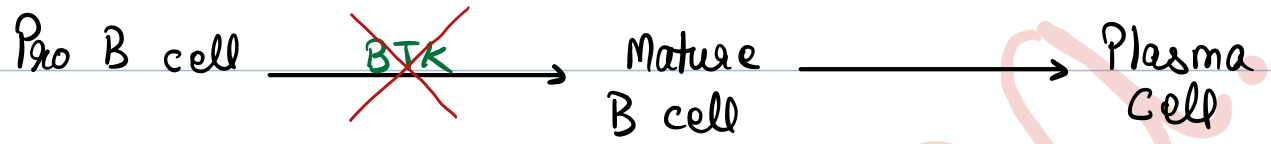
SECONDARY

- HIV
- Cancer
- Chemotherapy
- Malnutrition

Bruton's Agammaglobulenemia :

→ X-linked recessive disorder [male >>> female]

Pathogenesis: due to BTK gene defect [Bruton tyrosine Kinase]



→ decrease in mature B cells & plasma cells
→ defect in humoral immunity
→ T cells are normal
→ CMI intact

Histology of Lymph Nodes: Hypoplastic / Absent germinal centres

Clinical Presentation:

→ usually manifests after 6 months of age
→ recurrent • sinopulmonary infections
• enterovirus "
• giardia

Diagnosis: Flow cytometry
→ presence / absence of surface Ig's

Digeorge Syndrome: aka Velo (palate) cardio (CVS) facial (face) defects

→ del 22q 11 syndrome

↓

defect of TBx1

↓

defective development of 3rd & 4th pharyngeal pouches

↓

defective development of Thymus & Parathyroid

↓

- defective T-cell development
- Hypocalcemia

C - cleft lip, cleft palate
A - Abnormal facies
T - T cell defect, thymic hypoplasia
C - cardiac abnormalities [usually Tetralogy of Fallot]
H - Hypocalcemia
22 - del 22q 11

SCID [Severe Combined Immunodeficiency]:

→ defect in B cell, T cell & NK cell

Pathogenesis:

Two modes of inheritance
- X-linked recessive - more common
- Autosomal recessive - less common

Autosomal Recessive

↓

Deficiency of Adenosine Deaminase (ADA)
(ADA destroys the toxic metabolites of deoxy ATP)

↓

Accumulation of toxic metabolites

↓

Destruction of B, T, NK cells

X-linked recessive

↓

mutation in common γ chain of cytokine receptors

↓

reduced synthesis of IL-2, 4, 7, 11, 15

- defect in IL-4 (responsible for isotype switching) → decreased production of Igs
- decreased IL7 → decreased level of T lymphocytes
- decreased IL-15 → defect in NK cells

↓↓

SCID

Clinically: - increased risk of viral, protozoal, fungal, bacterial infections
- usually Candida infections or diaper rash.

→ first disease to be treated with gene therapy.

Ideal Treatment: hematopoietic stem cell transplant

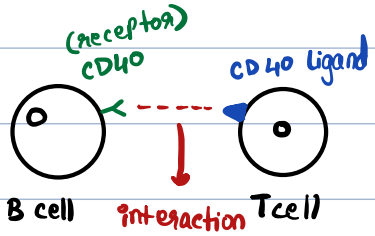
Hyper IgM Syndrome :

→ increased level of IgM

→ absence of class switching ∴ decreased level of IgG, IgA, IgE .

→ X-linked recessive mostly

Pathogenesis :



↓

production of plasma cell

↓

production of IgM

↓

class switching

↓

production of IgG, IgA, IgE

defect in CD40L or in CD40

↓

no class switching

↓

∴ excess IgM

less IgG, IgA, IgE

→ most common defect : CD40L

2nd " " " : CD40 .

Clinically:

increased IgM

- auto-immune thrombocytopenia
- " " hemolytic anemia
- " " neutropenia

decreased Ig G, A, E

increased risk of sinopulmonary infections

Common Variable Immunodeficiency [CVID]:

→ diagnosis of exclusion

Pathogenesis: mutation in BAFF gene

Pro B cell —BTK→ B cell —~~BAFF~~→ Plasma cell

↓

decreased plasma cells

↓

- decreased Ig's
- increased B cells ⇒ germinal centre hyperplasia

Isolated IgA Deficiency:

→ most common primary immunodeficiency disorder

→ reduced IgA, IgG2, IgG4.

Clinically: – increased risk of sinopulmonary / GI infections

– increased risk of anaphylatic Rx.

Wiscott Aldrich Syndrome:

→ X-linked recessive disorder

Pathogenesis: WASP gene defect on chromosome XP 11.23

helps in - cytoskeleton development
- T cell development
} ⇒ defective

Clinically: - **Triad**

i) Eczema

ii) Thrombocytopenia (& small thrombocytes)

iii) Immunodeficiency (due to defective T-cell development)

W - Wiscott, WASP gene defect
A - Aldrich
I - immunodeficiency
T - T cell defect, thrombocytopenia
} TRIAD
E - Eczema
R - reduced size & number of platelets / thrombocytes.
- recurrent infections

→ decreased Ig M
increased Ig A
normal Ig G
}

Ataxia Telangiactasia :

→ autosomal recessive

Pathogenesis : Defect in ATM gene on chromosome 11

Normally - DNA repair sensor ↓ activates p53

defect ↓ p53 is not activated ↓

- Ataxia telangiactasia
- Malignancies
- Premature aging
- Neurodegenerative disorders

Amyloidosis:

- pathologic
- proteinaceous (misfolded protein)
- extracellular
- hyaline
- eosinophilic substance

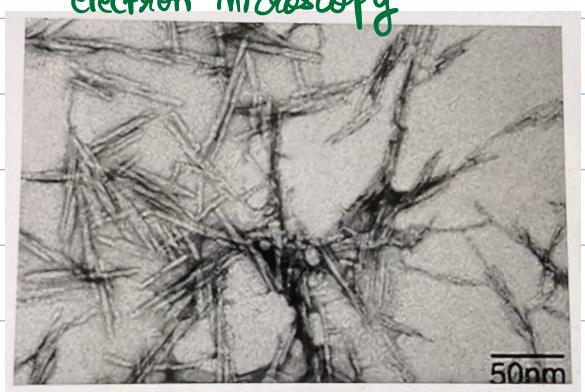
Physical Nature of Amyloid:

Electron microscopy

→ non-branching fibrils of indefinite length

→ 7.5 - 10 nm diameter

electron microscopy

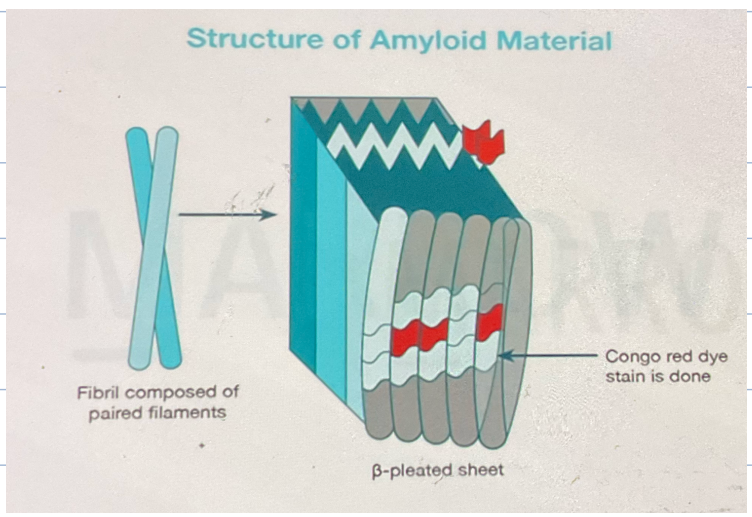


X-Ray Crystallography → Infrared Spectroscopy

→ cross β-pleated sheet structure.

⇓

responsible for apple green birefrengence of amyloid



Chemical Nature of Amyloid : A P protein

→ (Amyloid) A protein – 95 %

→ P protein – 5 % (depends on the disease)

Classification of Amyloidosis :

- **Localized**
  - → seen in specific organs & specific diseases
- **Generalised**
  - → seen in multiple organs
- **Familial**

Localized Amyloidosis :

① Medullary Ca of thyroid → A cal

- 95 % = amyloid protein
- 5 % = calcitonin

② Prion Disease → A Pr (Pr = prion)

③ Type II diabetes mellitus → A IAPP (islet associated pancreatic polypeptide)

④ Alzheimer's disease → A β

Generalized Amyloidosis:

Primary Amyloidosis: most common type of amyloidosis

→ seen in light chain disorders like multiple myeloma.

→ AL (L = light chain)

→ usually Lamda light chains are deposited

→ most common cause of death in primary amyloidosis: Heart Failure.

Secondary Amyloidosis: aka Reactive systemic amyloidosis.

seen in

- chronic inflammation conditions
- chronic neoplasms