MKT-IMMUNOLOGY CRASH COURSE

DR. ZAINAB VORA
MBBS, MD RADIOLOGY (AIIMS, NEW DELHI)

ACTIVE VS PASSIVE

when we give antigen (vaccine)/infec. body will mount a response against the antigen

- slow
- memory (+)

when we give antibodies directly

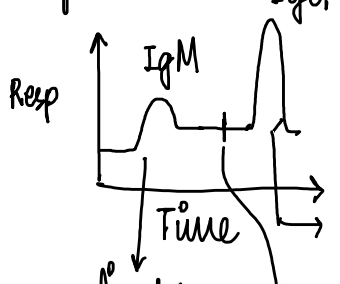
eg: 1. preformed Ig — eg: administered in hepatitis
2. maternal Abs

- faster
- transient (persists for 3 wks, then dies out)
- no memory

PRIMARY VS SECONDARY RESPONSE

response when exposed to antigen for the first time

↳ response to subsequent exposure to antigen



- first resp. takes time, IgM is 1st Ab to develop
- exposure to antibody for second time
- primary resp. is slow

↑ affinity

↑ avidity (because IgM, being a pentamer has multiple points of attachment)

AFFINITY VS AVIDITY

how strong Ag-Ab rxn is at one point

↳ when we consider strength of interaction at multiple points of attachment. So, more the no of binding points, more is the avidity.

INNATE VS ACQUIRED

type of immunity we are born with

↳ type of imm that we acquire later in life

Antigen presenting cell: - D: Dendritic cells - B - M

follicular Langerhans → in stratum spinosum (thickest layer) → lymph nodes → where HIV lives

Basale → Merkel cells, Melanocytes

	Innate immunity	Adaptive immunity
COMPONENTS	Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement, physical epithelial barriers, secreted enzymes	T cells, B cells, circulating antibodies
MECHANISM	Germline encoded	Variation through V(D)J recombination during lymphocyte development
RESPONSE TO PATHOGENS	Nonspecific Occurs rapidly (minutes to hours) No memory response	Highly specific, refined over time Develops over long periods; memory response is faster and more robust
SECRETED PROTEINS	Lysozyme, complement, C-reactive protein (CRP), defensins, cytokines	Immunoglobulins, cytokines
KEY FEATURES IN PATHOGEN RECOGNITION	Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs) and lead to activation of NF-κB. Examples of PAMPs: LPS (gram ⊖ bacteria), flagellin (bacteria), nucleic acids (viruses)	Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen → stronger, quicker immune response

NK cell=LGL=Null cell= large granular lymphocyte; neither T nor B
MHC unrestricted cell
↳ don't need MHC for activ unlike B & T
Inhibitory: MHC I
Stimulation: IL2, 12, 15 (also in Th)
CD: 16, 56, 94 → INI Q
automatically activated by cytokines
inhibited when there ↓ MHC I
SRK started acting at 16, did Pathaan at 56, & we hope he acts till 94

Nod-like receptors- mediate necrosis & pyroptosis
Mutations NOD2- a/w periodic fevers, IBD, DM
RIG-STING pathway:
↳ for viral cell death
Antivirals → Interferon (α, β, γ)
part of RIG STING pathway
α, β → antiviral (antiBiral)
γ → ↳ granuloma

Immune privilege:
↳ pouli T weak immune system
1. eye
2. brain & blood brain barrier
3. testis
4. placenta

TLR 4 → GRAM - 4 letters
↳ TLR 3 (DNA - 3 letters)
TLR 5 (FIVE)

α Leucocyte
β Fibroblast
γ T lymphocyte (TH1)

"patriotism"

MHC I is present in all nucleated cells
so, MHC I is the "tag" of self cells.
Natural killer cells will kill the cells ↓ MHC I and spare the ones ↑ MHC I

"Pathaan"

virus affected cell

cancer cell

RBC does not have its own MHC I. It protects itself from getting killed by NK cell by adsorbing MHC-I from elsewhere

	MHC I	MHC II
LOCI	HLA-A, HLA-B, HLA-C MHC I loci have 1 letter	HLA-DP, HLA-DQ, HLA-DR MHC II loci have 2 letters
BINDING	TCR and CD8	TCR and CD4
STRUCTURE	1 long.chain, 1 short chain	2 equal-length chains (2 α, 2 β)
EXPRESSION	All nucleated cells, APCs, platelets (except RBCs)	APCs
FUNCTION	Present endogenous antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells	Present exogenous antigens (eg, bacterial proteins) to CD4+ helper T cells
ANTIGEN LOADING	Antigen peptides loaded onto MHC I in RER after delivery via TAP (transporter associated with antigen processing)	Antigen loaded following release of invariant chain in an acidified endosome
ASSOCIATED PROTEINS	β_2-microglobulin	Invariant chain
STRUCTURE		

most imp HLA matching for transplant
LDR is most imp for transplant

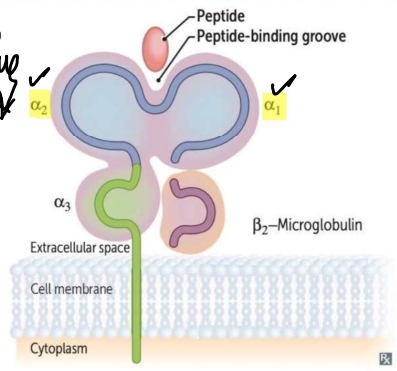
- MHCs are proteins
- encoded by HLA genes
- HLA on chr. 6p
HFE is also on 6p

Parts of HLA:

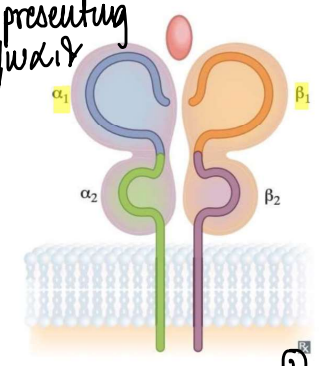
I → A/B/C, E, G (1 letter)
III → does not code for MHC
II → DP, DQ, DR (2 letters)

- codes for complement related proteins
  1. HSP (heat shock protein)
  2. early complement factors
  3. TNF α

antigen presenting site is b/w α_1 & α_2



antigen presenting site is b/w α_1 & β_1



Rule of 8's

① MHC I presents to CD8 (1 × 8 = cytotoxic)
MHC II presents to CD4 (2 × 4 = helper)

② CD4 : CD8 = 2 : 1
↓
If BAL shows ↑ ratio → sarcoidosis **

HLA subtypes associated with diseases

HLA SUBTYPE	DISEASE	MNEMONIC
B27	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis	PAIR
B57	Abacavir hypersensitivity	
DQ2/DQ8	Celiac disease	I ate (8) too (2) much gluten at Dairy Queen
DR3	DM type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease	DM type 1: HLA-3 and -4 (1 + 3 = 4) SL3 (SLE)
DR4	Rheumatoid arthritis, DM type 1, Addison disease	There are 4 walls in 1 "rheum" (room)

	B CELL	T CELL
%	20%	70%
Immunity	Humoral	CMI
Formation	Bone marrow	Bone marrow
Maturation	Bone marrow	Thymus
LN	Cortex (B cell - babar)	Para cortex
Spleen	Cortex	PALS (peri arteriolar lymphoid sheath)
GIT	Peyer's patches	Intraepithelial T cells → ↑ in celiac dfs
CD Markers	Markers: CD 10 = CALLA (common ALL antigen) • CD 19, 20, 21, 22, 23 • CD 40 • CD 79a / 79b Pan B cell: CD 19 Signal transduction: 79a, 79b BCR: ↳ antibodies ↳ M – IgM D – IgD	Markers: 1-8, 28, 40(L) ↳ L = ligand ↳ imp for costimulatory signal Pan T cell: 3 Signal transduction: 3 TCR: αβ chain (90% of T cells (R)) ~~99~~ # γδ → GI tract, GU tract → non MHC dep CD4 : CD8 ↳ 2:1

(10% → NK cell (non B non T = null cell)

T cells	TCR (binds antigen-MHC complex), CD3 (associated with TCR for signal transduction), CD28 (binds B7 on APC) → costim signal
Helper T cells	CD4, CD40L, CXCR4/CCR5 (coreceptors for HIV)
Cytotoxic T cells	CD8
Regulatory T cells	CD4, CD25, FoxP3 → Treg cells → as they are immuno suppressive → derangement causes IPEX syndrome
B cells	Ig (binds antigen), CD19, CD20, CD21 (receptor for Epstein-Barr virus), CD40, MHC II, B7 (CD80/86)

αβ

pan T cell signal transd.!!

Types of TCR: αβ / γδ

"best prognosis is when 2 people study together"

NHL → CD 3+ → T cell

CD 19/20 + (pan B cell marker)

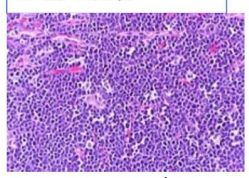
CD 10 +
BCL-2 +

Follicular lymphoma
- best prognosis

CD 10 +
BCL6 +

+ on chr 8

C-myc
Ki 67 100%



- hypercellular
- starry sky appearance

Burkitt's lymphoma
- H/O child ↑
- jaw swelling, abdominal swelling

b/c large

MC NHL
MC aggressive
MC extranodal

DLBCL

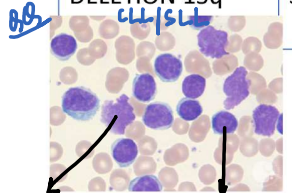
PEL-CD 30/38+
HIV-EBV

PEL = primary effusion lymphoma

CD 5 +

CLL/SLL

CD 23+
Cd 200+
DELETION 13q



smudge cells lymphocytes

CD 23-
CYCLIN D1 → chrom 11 x2 -|
SOX 11

Mantle cell lymphoma

CLL: convent school girl appearance
[convent school girls wear same uniforms, all cells look the same]

CML: college party girl appearance
[college girls wear diff. clothes, cells look different]

different lineages

- MC in elderly
- MC in West

} CLL

CD5-
CD 23-
CD 10-

Marginal zone lymphoma

[push negative people to the side 😐] → -ve people are marginalised

- any lymphoma developing in a setting of chronic inflammation → usually MALToma

eg: Sjogren, thyroiditis, chronic inflamm^n in stomach

- antigen presenting cells
- come thro' med. loods

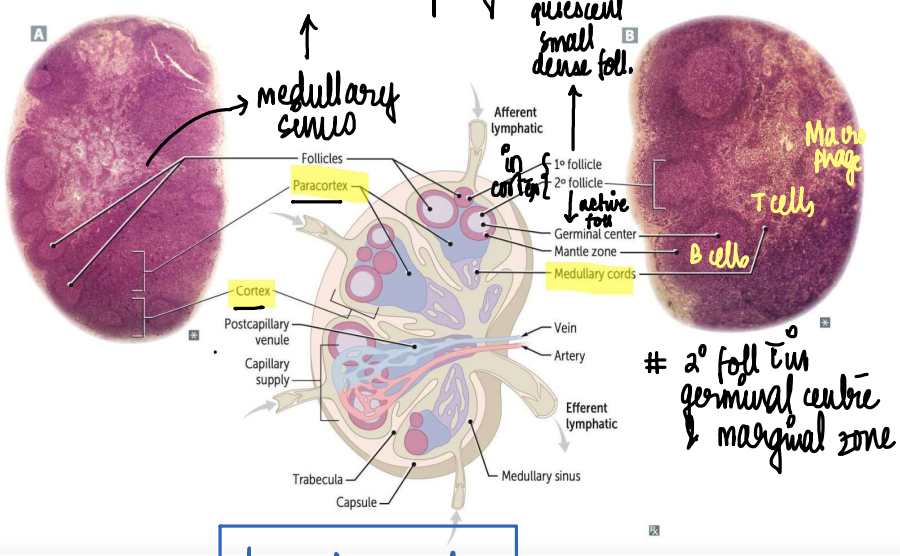
↑

contain macrophages

↑

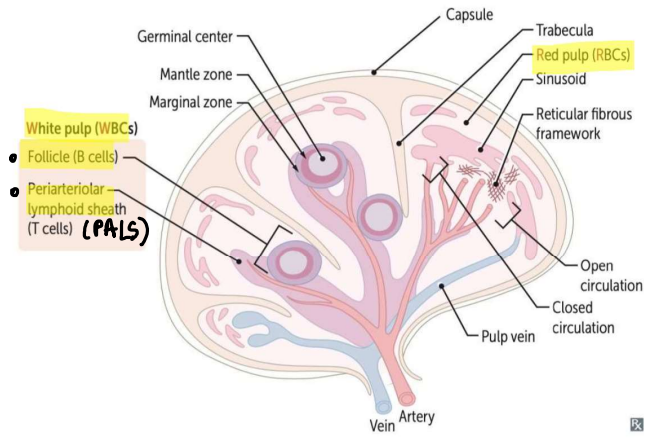
medullary sinus

quiescent small dense foll.



2° foll in germinal centre & marginal zone

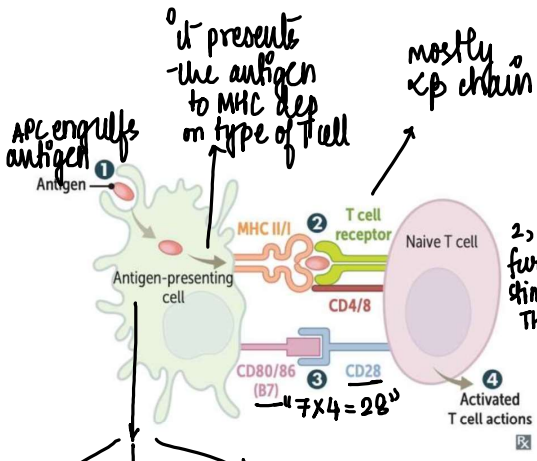
Lymph node



Spleen

antigen presenting cell

B cells	Humoral immunity. Recognize and present antigen—undergo somatic hypermutation to optimize antigen specificity. Produce antibody—differentiate into plasma cells to secrete specific immunoglobulins. Maintain immunologic memory—memory B cells persist and accelerate future response to antigen.
T cells	Cell-mediated immunity. CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes. CD8+ T cells directly kill virus-infected and tumor cells via perforin and granzymes (similar to NK cells). Delayed cell-mediated hypersensitivity (type IV). Acute and chronic cellular organ rejection. **Rule of 8**: MHC **II** × CD**4** = **8**; MHC **I** × CD**8** = **8**.



°it presents the antigen to MHC dep on type of T cell

mostly cp brain

APC engulfs antigen

"7x4=28"

2,12 further stimulate TH1

T-Helper cell: E has 4 lines

TH1 → makes IL2, IL12, IFNγ → granuloma

TH2 ↑ granuloma
4 – IgE, mast cell
5 – eosinophil, IgA class switch
13 – mucus ↑, ↑↑ IL4 prodⁿ, mast cell
10 – immunosuppressant ↓ imm resp

TH17 → produces IL17 → ↑ neutrophil migration

(2,12,15 → NK ; 15 sp for NK)

Cytotoxic T cell (CD8)
- granzymes, perforins → also in NK cell → perforins perforate & insert granzymes to kill the cell
- Fas/FasL → cell to be killed (CD95) – Fas ind. by CD8 → Fas-FasL binding → apoptosis

TREG cell: (ind by CD8)
- brings down imm resp → produces immunosupp cytokine (IL10)
- markers: CD25, FOXP3

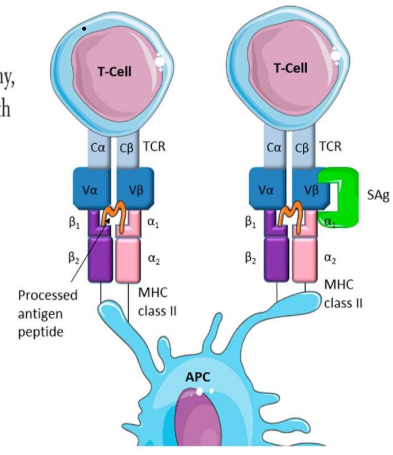
D → dendritic cell → Langerhans
- follicular → most potent

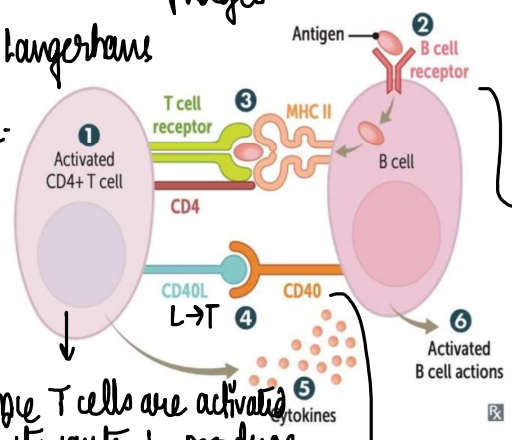
B → B cell

M → macrophages

"u need 2 interactⁿ to fall in ♡"

IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome—genetic deficiency of FOXP3 → autoimmunity. Characterized by enteropathy, endocrinopathy, nail dystrophy, dermatitis, and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants.





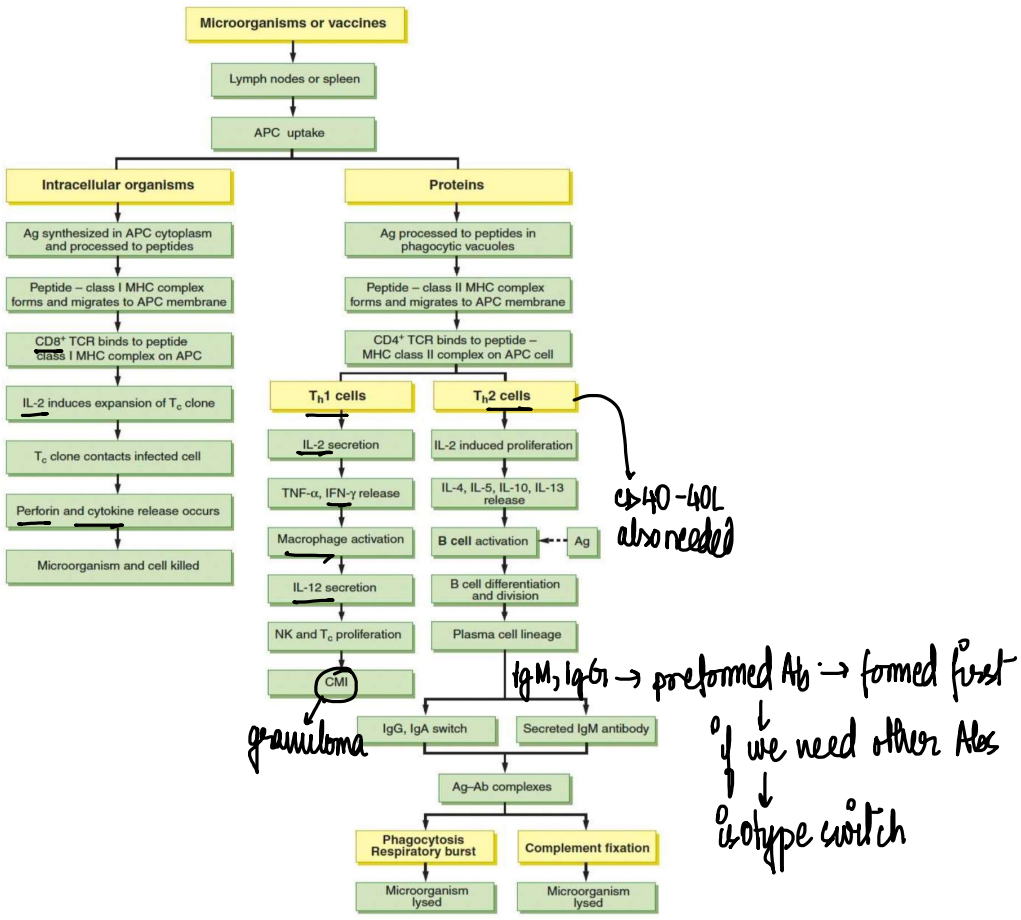
°if B cell acts as APC, it can also act via MHC-II TCR to stimulate cytotoxic T cell

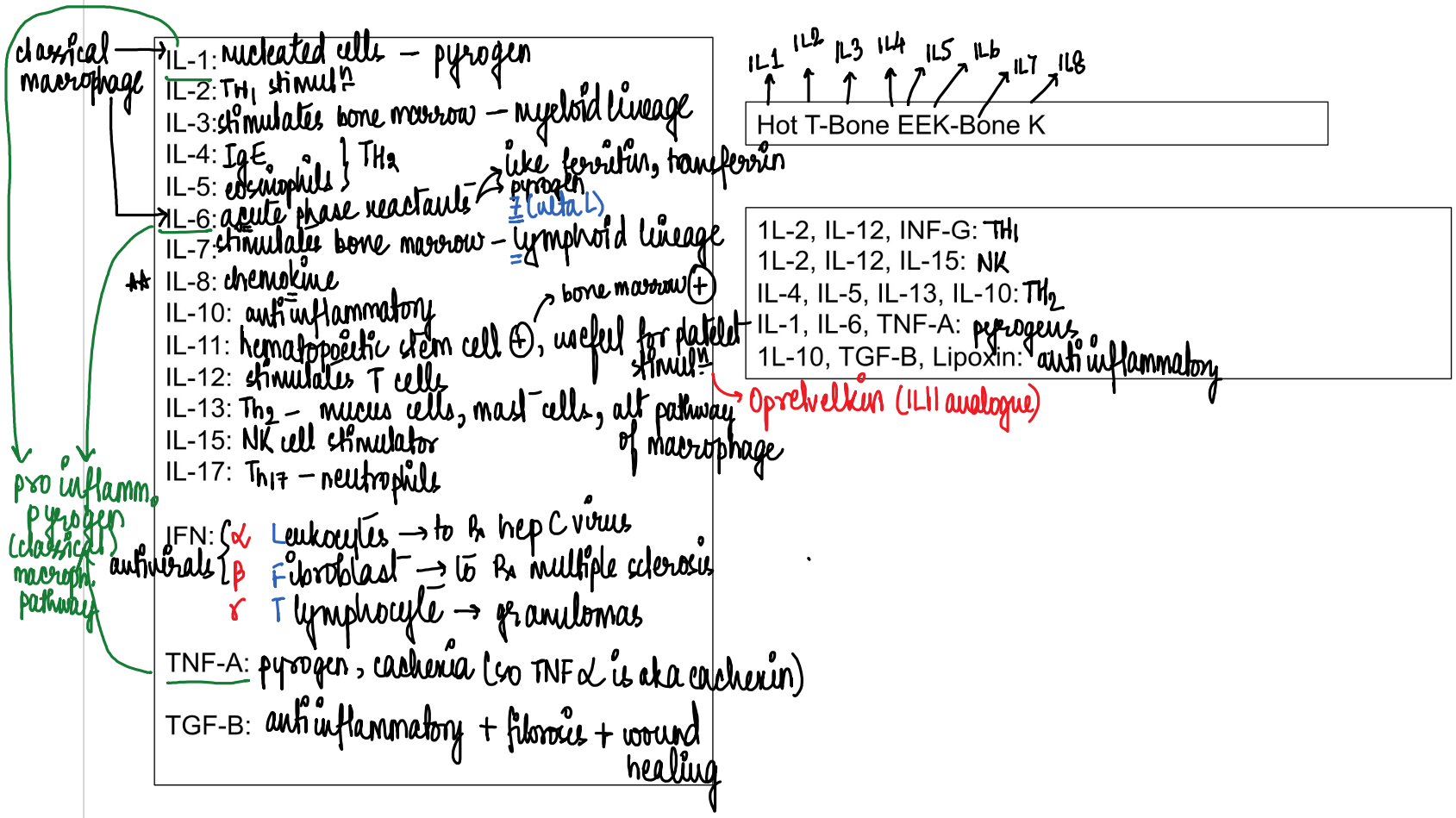
costimulatory signal → # costimulatory signal for APC → B7, 28

opp T cells are activated & it wants to produce IgA, IgE, it has to stimulate B cell by T cell (R) – MHC II of B cell binding

Ag – have to be destroyed
↓
caught by APC [DBM]
↓ ↑ B7; CD28
taken to naive T cell to stimulate it
- if endogenous Ag → CD8 (MHC I)
- if proteinaceous Ag → CD4 (MHC II)

↓
T cell matures
- cytotoxic
  - perforin granzyme
  - Fas–FasL → apoptosis
- helper → does it need CMI or humoral?
  - CMI → convert to TH_1 → granuloma (C2, C3, IFNγ)
  - humoral → convert to TH_2 → IL4, 5, 13
  - TH_{17} → will bring neutrophils

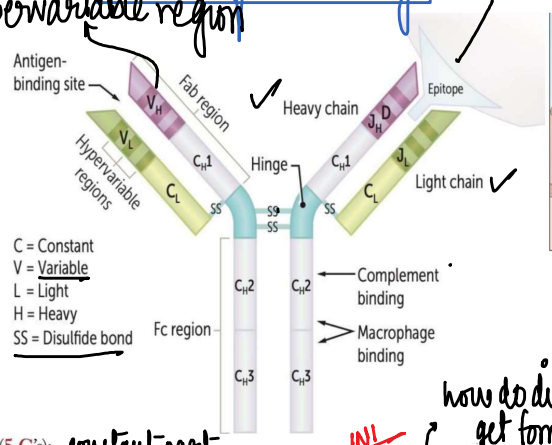

Microorganisms or vaccines
Lymph nodes or spleen
APC uptake
Intracellular organisms
Proteins
Ag synthesized in APC cytoplasm and processed to peptides
Peptide – class I MHC complex forms and migrates to APC membrane
CD8+ TCR binds to peptide class I MHC complex on APC
IL-2 induces expansion of Tc clone
Tc clone contacts infected cell
Perforin and cytokine release occurs
Microorganism and cell killed
Ag processed to peptides in phagocytic vacuoles
Peptide – class II MHC complex forms and migrates to APC membrane
CD4+ TCR binds to peptide – MHC class II complex on APC cell
Th1 cells
Th2 cells
IL-2 secretion
IL-2 induced proliferation
TNF-α, IFN-γ release
IL-4, IL-5, IL-10, IL-13 release
Macrophage activation
B cell activation
Ag
IL-12 secretion
B cell differentiation and division
NK and Tc proliferation
Plasma cell lineage
CMI
IgG, IgA switch
Secreted IgM antibody
Ag–Ab complexes
Phagocytosis Respiratory burst
Complement fixation
Microorganism lysed
Microorganism lysed
CD40-40L also needed
granuloma
IgM, IgG1 → preformed Ab → formed first
if we need other Abs
isotype switch

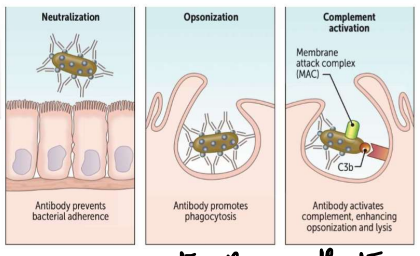

classical macrophage
IL-1: nucleated cells – pyrogen
IL-2: TH1 stimuln
IL-3: stimulates bone marrow – myeloid lineage
IL-4: IgE, eosinophils } TH2
IL-5:
IL-6: acute phase reactants – like ferritin, transferrin
pyrogen
+ (ulta L)
IL-7: stimulates bone marrow – lymphoid lineage
IL-8: chemokine
IL-10: anti inflammatory
IL-11: hematopoietic stem cell +, useful for platelet stimuln
bone marrow +
IL-12: stimulates T cells
IL-13: Th2 – mucus cells, mast cells, alt pathway of macrophage
IL-15: NK cell stimulator
IL-17: Th17 – neutrophils
IFN: α Leukocytes → to Rx hep C virus
β Fibroblast → to Rx multiple sclerosis
γ T lymphocyte → granulomas
antivirals
TNF-A: pyrogen, cachexia (so TNF α is aka cachexin)
TGF-B: anti inflammatory + fibrosis + wound healing
pro inflamm, pyrogen (classical) macroph. pathway
IL1 IL2 IL3 IL4 IL5 IL6 IL7 IL8
Hot T-Bone EEK-Bone K
1L-2, IL-12, INF-G: TH1
1L-2, IL-12, IL-15: NK
IL-4, IL-5, IL-13, IL-10: TH2
IL-1, IL-6, TNF-A: pyrogens
1L-10, TGF-B, Lipoxin: anti inflammatory
Oprelvekin (IL11 analogue)

Ig are glycoproteins (they have carbs) = site for Ag binding specific to Ab - dft hypervariable region

dense band = hypervariable region

Parts of antibody





coats antigen so that phagocytes can eat it

activates complements - binding site = C_{H2}

Fc (5 C's): constant part
- Constant
- Carboxy terminal
- Complement binding - CH_2 [2,3 → macrophage binding]
- Carbohydrate side chains
- Confers (determines) isotype (IgM, IgD, etc)

determines isotype

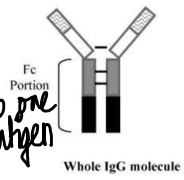
Isotype: GAMDE
Allotype: IgG1,2,3,4
Idiotype: Ag binding site specificity

"Idiots are specific"

how do diff antibodies get formed

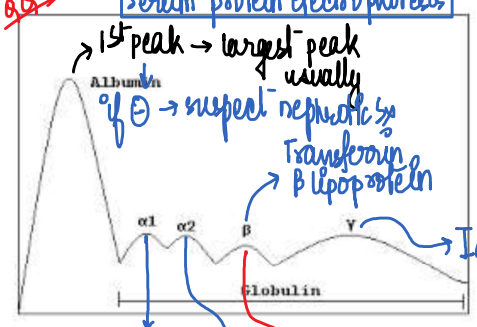
Generation of antibody diversity (antigen independent)
1. Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes by RAG1 and RAG2
2. Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
3. Random combination of heavy chains with light chains

Generation of antibody specificity (antigen dependent) → that antibody will bind only to one part. antigen
4. Somatic hypermutation and affinity maturation (variable region)
5. Isotype switching (constant region)



- There are 3 heavy chains for 3 Ab → IgG, IgA, IgD (we take more for ME)
- 4 heavy chains for 2 Ab → IgM, IgE

Serum protein electrophoresis



1st peak → largest peak usually

↓ in Θ → suspect nephrotic syn

Transferrin

β Lipoprotein

Ig → γ spike is due to the protein part of Ig

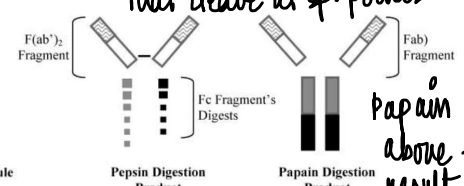
↑ in multiple myeloma

Θ in α1 antitrypsin deficiency

α2 macro globulins
- ceruloplasmin
- haptoglobin

β broad β band is seen in type 3 hyperlipoproteinemia

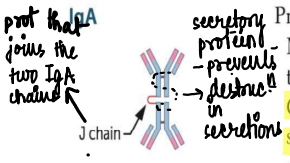
Pepsin & papain are proteases that cleave at sp. points



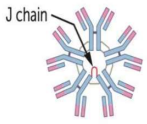
Papain cuts above → result of cleavage → 2 Fab, 2 Fc

pepsin cuts below, so the variable portion remains attached, & the constant part is cleaved

IgG — Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity that starts to wane after birth). "IgG Greets the Growing fetus." Associated with warm autoimmune hemolytic anemia ("warm weather is Great!").

IgA — 

Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement. Monomer (in circulation) or dimer (with J chain when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (eg, by Peyer patches) and protects against gut infections (eg, Giardia). Most produced antibody overall, but has lower serum concentrations. Released into secretions (tears, saliva, mucus) and breast milk. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases.

IgM — 

Produced in the 1° (IMmediate) response to an antigen. Fixes complement. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves. Associated with cold autoimmune hemolytic anemia.

IgD — 
Unclear function. Found on surface of many B cells and in serum.

IgE → IL4 (+) — 
Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to parasites by activating Eosinophils.

Concentration: G1 > A > M > D > E
t1/2: G1 > A > M > D > E
Heat tolerance: G1 > A > M > D > E
Classical Complement: MG1 → "MG1 ears are classical"
Alternate Complement: IgA
Ag receptor: IgM, D → we will become receivers of MD"
Homocytotropic Ab: IgE
Reagnic Ab: IgE

parasite

↓

APC takes it to TH_2

↓

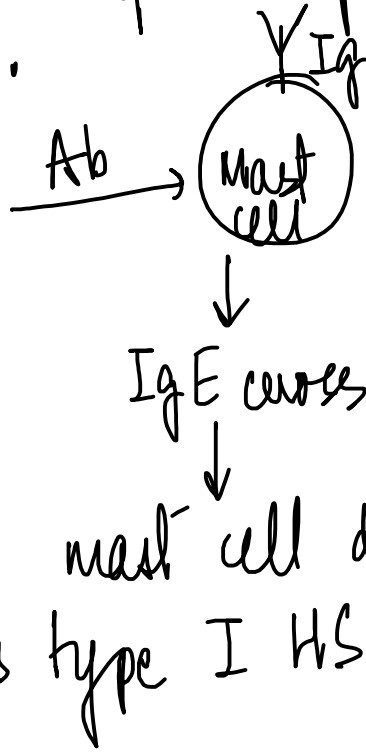
IL4 5 13

↓

↑eosino phil ↑mucus ↑mast cell

[strongest stim of mast cells = IL4]

This takes time in 1st exposure but in subsequent exposures, the mast cell is ready.



↓

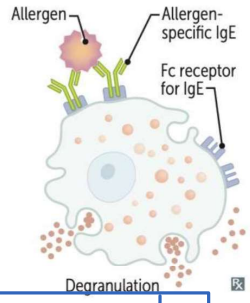
IgE crosslinking

↓

mast cell degranul^{n}

This is type I HS

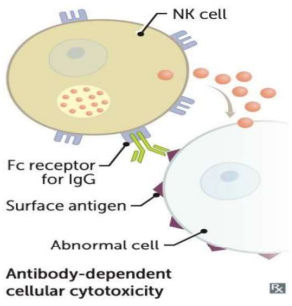
Type I H/S



- allergies
- anaphylaxis
- asthma
- atopy
- applied in Casoni's test for hydatid cyst
- VKC } type I H/S is implicated here
- ABPA }

Type II H/S

- Antibody mediated cytotoxicity



Examples: (blood related)
- Autoimmune hemolytic anemia (including drug-induced form) (coomb's test)
- Immune thrombocytopenia
- Transfusion reactions
- Hemolytic disease of the newborn

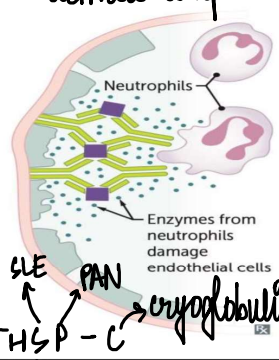
Examples: Ig activates complements
- Goodpasture syndrome → anti GBM Ab
- Rheumatic fever
- Hyperacute transplant rejection

Examples: Type II H/S → receptor destruction
- Myasthenia gravis (AchR)
- Graves disease (TSHR = LATS = TSI) → antibody

→ opsonises → activate complement pathway → induces phagocytosis by macrophages, NK cells

Type III H/S

- Immune complex
- Ag + Ab float in blood & meet - form a complex
- activate complement



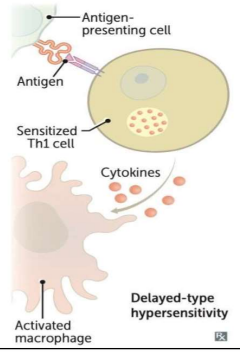
HSP SLE PAN HSP-C → cryoglobulinemia

- SLE
- Rheumatoid arthritis
- Reactive arthritis
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis
- IgA vasculitis = HSP

- arthrus rxn = localised type III rxn
- serum sickness

Type IV H/S

- Th1 pathway
- cell med immunity
- granulomas (IL2, IL12, TNFα)



Examples:
- Contact dermatitis (eg, poison ivy, nickel allergy), artificial jewellery, washerwoman's hand
- Graft-versus-host disease

Tests: PPD for TB infection; patch test for contact dermatitis; *Candida* skin test for T cell immune function.

4T's: T cells, Transplant rejections, TB skin tests, Touching (contact dermatitis).

- checking delayed H/S
- Mantoux test → TB
- Lepromin test → leprosy
- Montenegro " → kala azar
- patch test

RA → III > IV

HSP → III, IV

SLE → III > II

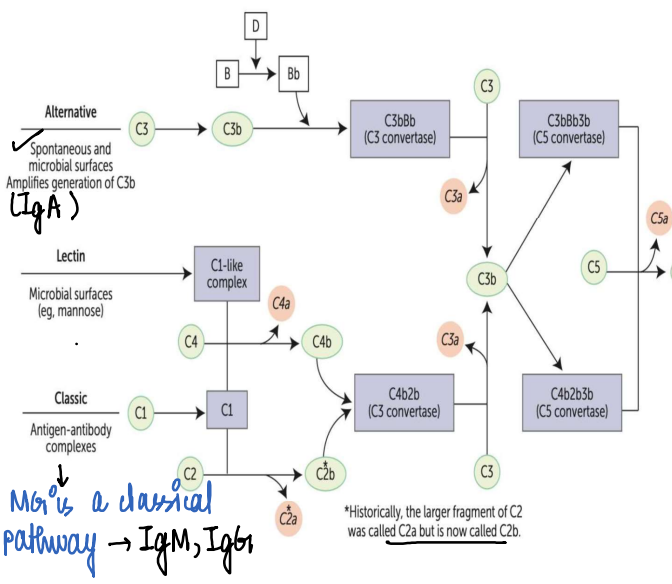
ABPA → I > III, IV

Hyperacute → type II (preformed Abs)

Acute → II, IV
(humoral) (CMI)

Chronic → IV

complement pathway



C1 → C2b / C4b → C3b → C5b → 6, 7, 9

Terminal complement

Lysis, cytotoxicity

If ↓ def, complement is activated

- C3b—opsonization.
- C3a, C4a, C5a—anaphylaxis.
- C5a—neutrophil chemotaxis.
- C5b-9 (MAC)—cytolysis. → kill

Opsonins—C3b and IgG are the two 1° opsonins in bacterial defense; enhance phagocytosis. C3b also helps clear immune complexes.

MC complement deficiency: C2

Early comp def: SLE

Terminal comp /MAC def: Neisseria

CD55/59 deficiency: PNH → RBC destruction ↑ d/t persistent complement activation

Factor H/I/CD46 def: atypical HUS

C1 INH def: Her angioedema (↓ ACE⊖ ↓ C4)

Test for classical comp: CH50

IBD – pt c swollen eyelids, lips → fatal → there can be laryngeal edema

O157:H7 → classical HUS

In HAE, bradykinin ↑ ACE⊖ will further ↑ bradykinin (kallikrein pathway stimulated)

chemokines
- IL8
- C5a

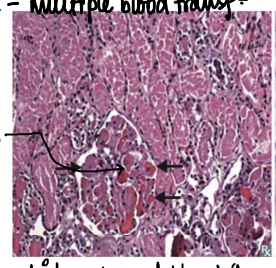
↓ "call neutrophils"

opsonins
- IgG1
- C3b

TRANSPLANT IMMUNOLOGY

Hyperacute (type II H/S)

- in mins (rate at first sight)
- preformed Abs (girl has bad exp in past so she has given up on D)
- multiparous ♀ } multiple rel^{n} in the past
- multiple blood transf^{n}

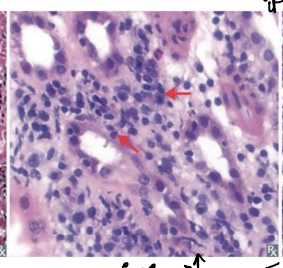


- kidney turned blue & floppy right after transplant (5 secs)
- thrombosis on biopsy (pathologist sees)
- coagulative necrosis of organ
- fibrinoid " " vessel

Acute rejection

- Initially yes, few wks – months later – no [wks – months]
1. Humoral – type II →
2. CMI – type IV

If we do a transplant of a kidney that is not completely HLA matched, the antigen that did not match will be presented by the APC of donor kidney & the body will mount a response against



- Tubulitis → lymphocytes
- Inflamm^{n}

Chronic → >6 months

(not working even after marriage) → everything fibrosed & atrophied

- CMI – type IV H/S
  - G – GBM duplic^{n}
  - O – obliterative phlebitis
  - T – tubular atrophy
  - I – intimal fibrosis
- self APCs

HPE finding of Ig4 related
- OB phlebitis
- storiform fibrosis
- lymphoplasmacytic infil^{n}

chronic reflec^{n}

Organ-specific examples:
- Chronic allograft nephropathy
- Bronchiolitis obliterans
- Accelerated atherosclerosis (heart)
- Vanishing bile duct syndrome

Marker of acute humoral rejection: C4d

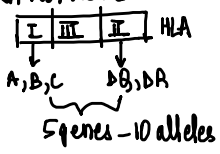
C4d deposition indicates that antibodies & complements have come into picture

- **Orthotopic graft:** Donor organ transplanted to the diseased organ site- **liver.**
- **Heterotopic graft:** Donor organ transplanted at a site different from normal anatomical position. **Kidney** in iliac fossa, **pancreas, PTH**

Humby's knife
↑
partial thick. full thick.

Autograft- when we transfer eg: skin graft
Isograft- graft from own body
Allograft/Homograft- identical twin
Xenograft/Heterograft- same species
diff " eg: bovine heart valve

Blood group matching: mandatory (only ABO, Rh not needed)
HLA matching:
Most important match: DR (DR is always the most imp in transplant Sx)
Ideal- B|10 – A,B,C,DB,DR
Practical- 6|8 – A,B,C,DR
Child- 4|6 → A,B,DR
HLA match not needed: (cornea, skin (avascular), heart, lung, liver (viability > matching))



5 genes – 10 alleles

Grafted immunocompetent T cells proliferate in the immunocompromised host and reject host cells with "foreign" proteins → severe organ dysfunction	Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly
HLA mismatches (most importantly HLA-A, -B, and -DR antigens) ↑ the risk for GVHD	Usually in bone marrow and liver transplants (rich in lymphocytes)
Type IV hypersensitivity reaction	Potentially beneficial in bone marrow transplant for leukemia (graft-versus-tumor effect)
	For patients who are immunocompromised, irradiate blood products prior to transfusion to prevent GVHD

GIT → liver

here we want graft donor T cells to come & kill host tm cells (GVHD & leukaemia)

GVHD

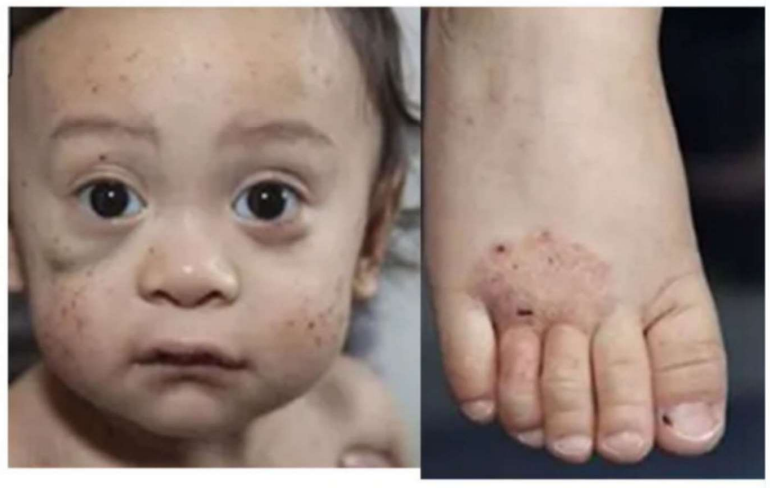
eg: bone marrow graft in immunocompromised person – bone marrow – HSC transplant – immunocompetent cells in graft – proliferate & attack host cells – severe organ dysfun^{n}

(guy marries innocent girl – and destroys her)

Printout

Tuesday, January 31, 2023 11:12 AM

Bleeding from umbilical stump
Normal-Low IgG, IgM
High IgA, IgE



WISKOTT ALDRICH SYNDROME

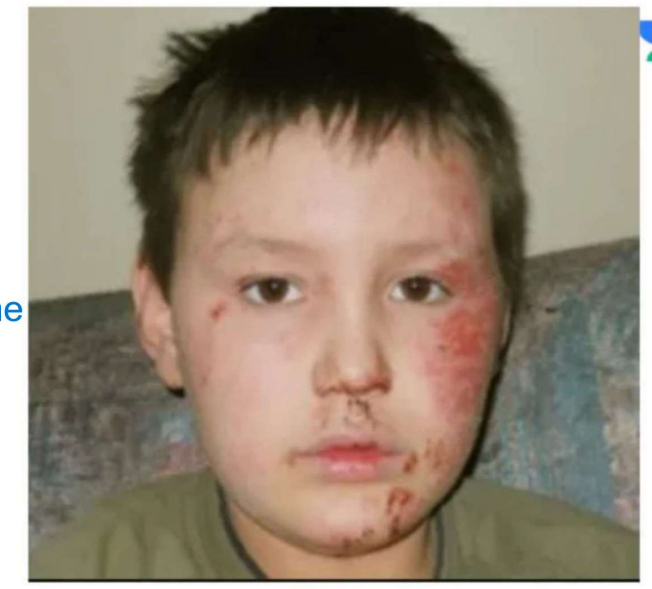
Wiscute Aldrich- cute baby
Wiscute with a TIE
T- thrombocytopenia
I- immunodeficiency
E- eczema
repressed boy, XLR
WASP- affects cytoskeleton
1. APC
2. Platelet

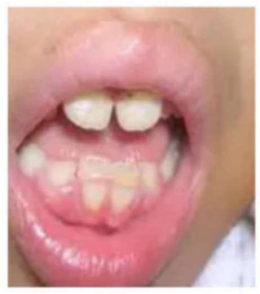
Eczema

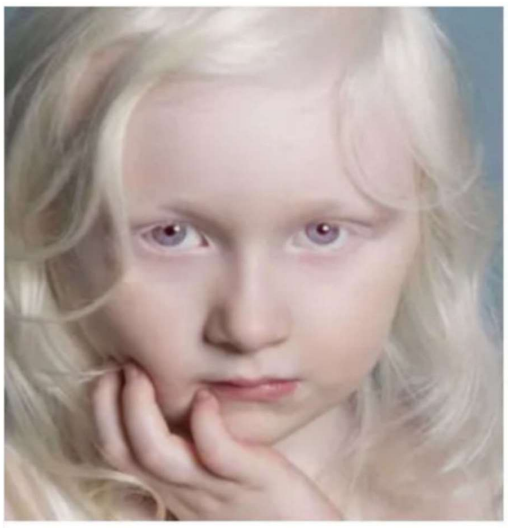
High IgE, eosinophilia

when he turns 17, he will become dominant and needs job stat, and he is FATEd to become successful
- cells affected: Th17
- STAT3 gene
- AD

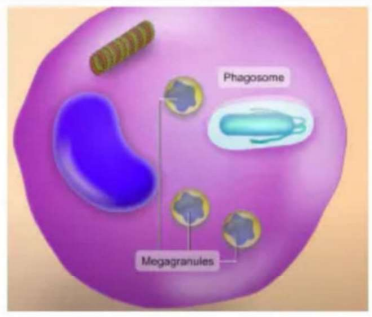
This is JOB syndrome
F- abnormal facies
A- multiple cold abscesses
T- teeth- retains primary dentition
E- igE, eosinophils, eczema
↳ deep set eyes
↳ broad forehead

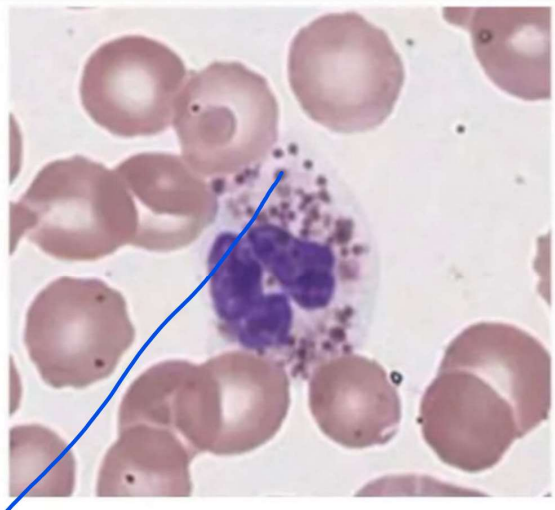






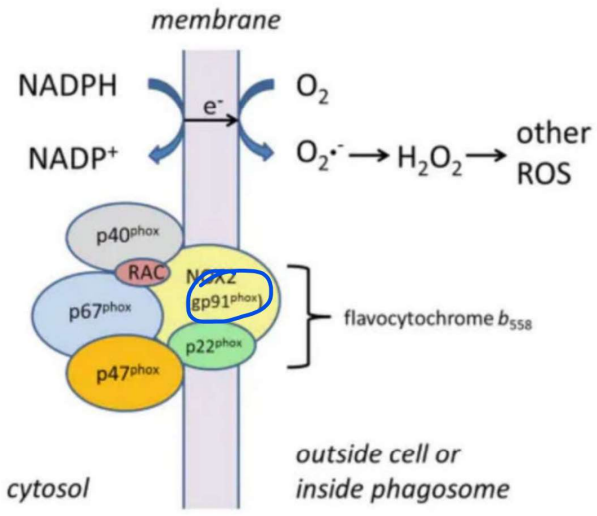
Albinism





giant granules in neutrophils

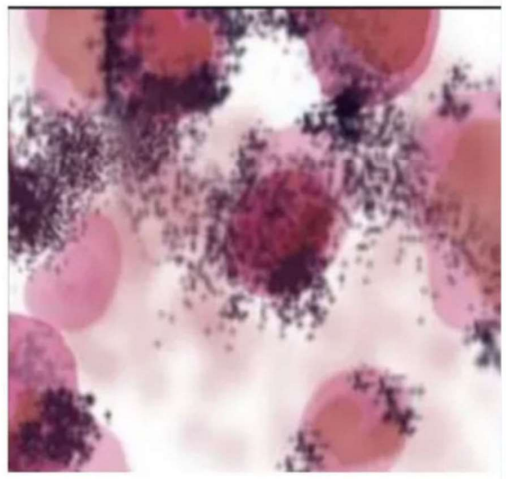
she is a girl: lost pigments- became recessive
cannot be X linked- so autosomal
This is CHEDIAK HIGASHI
In life she has a LYST to study alphabets- LMNOP
L- light hair, lymphohistiocytosis
LYST fun ↓
M-microtubule function lost
N- neuropathy, neurodegeneration, neutrophil shows giant granules
O- phagOlysosome fusion
P- platelet has dense granules, pancytopenia



Chronic granulomatous ds
- MC; GP91
- XLR, AR
- test: NBT test
- C: catalase positive org infection
eg: Serratia, S aureus, Candida, Pseudo, Aspergillus
- G: granulomatous
- D: DHR test: flow cytometry (IOC)

↓
dihydrorhodamine

NBT = nitro blue tolunidine test



normal: NBT
if blue missing- CGD

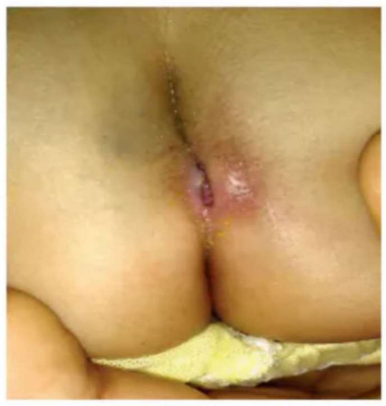
CGD + anemia

G6PD deficiency

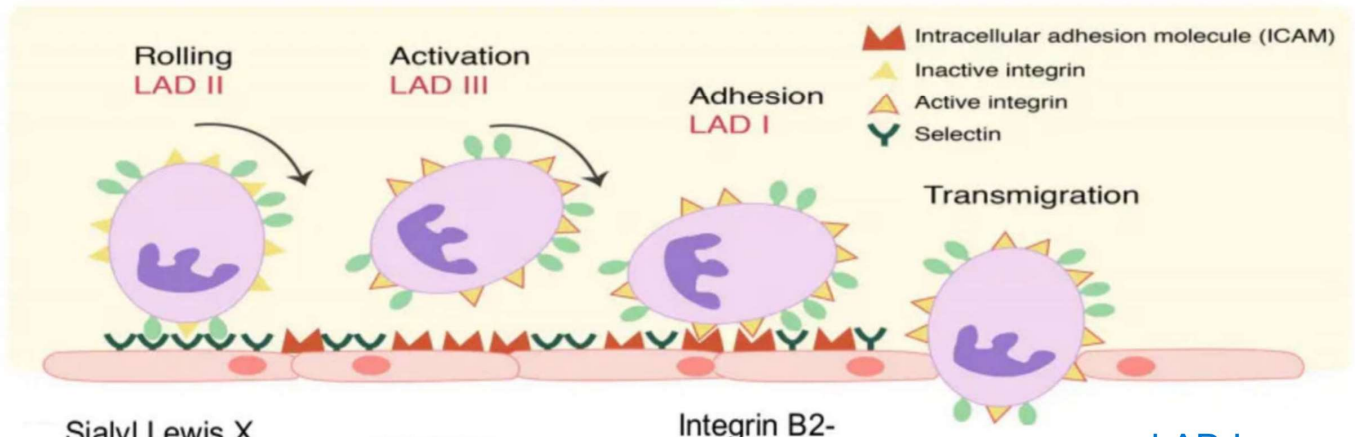
NO PUS
NEUTROPHILIA
OMPHALITIS

LAD type 1
- LADs are mama's boys: AR
L: late umb cord separation
A: Absent pus
D: dysfunctional neutrophils

no separation
of umb cord



Leukocyte Adhesion Deficiency Types I-III



Sialyl Lewis X Deficiency

FERMT3

Integrin B2-CD 18

Fucosyl transferase deficiency

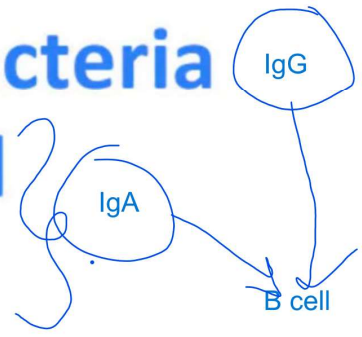
LFA1/MAC1

LAD II: RoLLing- Selectin
Sialyl Lewis
Fucosyl
bombay blood group

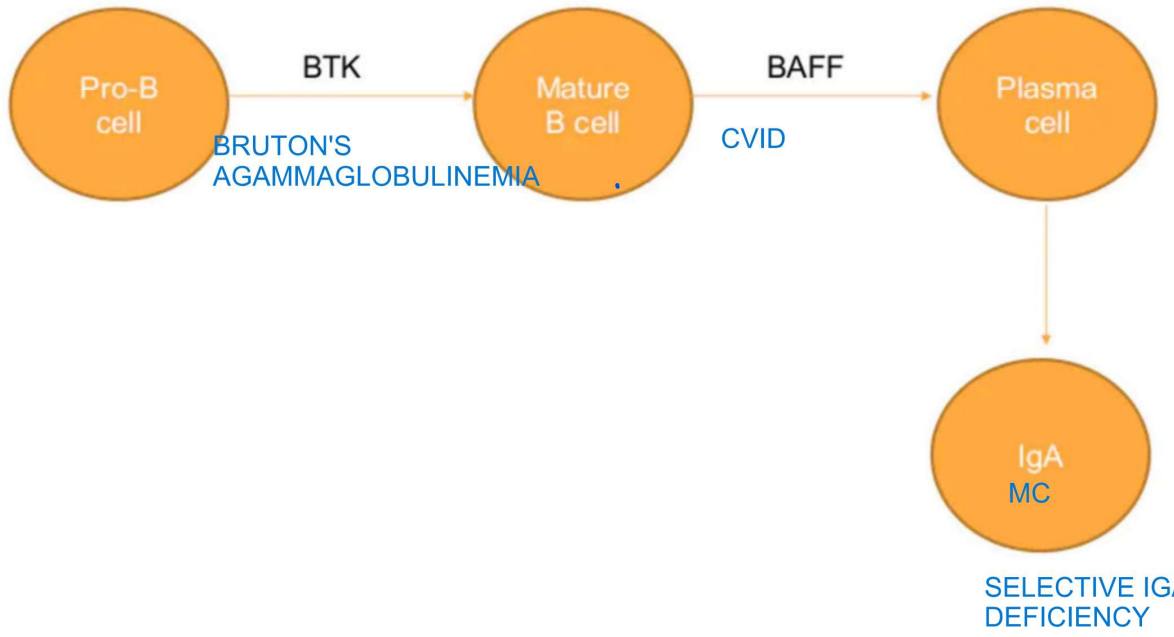
LAD III:
grape juice FERMented
on drinking we get ACTIVE
(ACTIVation defect)
hallmark: bleeding

LAD I
INTEGRIN
1-8
LFA1, MAC1

Encapsulated bacteria
Enteroviral
Giardia



High R/o AI diseases


Pro-B cell
BTK
Mature B cell
BAFF
Plasma cell
BRUTON'S AGAMMAGLOBULINEMIA
CVID
IgA MC
SELECTIVE IGA DEFICIENCY

After 6 months

Absent Ig-all

Absent germinal centres

since no B cells

BRUTON'S

because here only B cell and Ig is defective so baby can function for 6 months with maternal antibodies
Hence this manifests after 6 months

SCID- no B cell, no T cell
so presents before 6 months

B- BRUTON- boys- XLR

Adolescent
Hyperplastic germinal centre
All Igs low

mature B cell is present but plasma cell cannot be formed

↓

CVID

- BAFF
- sporadic
- family history: selective IgA deficiency

BT reaction-anaphylaxis
Urine pregnancy test false+
Giardiasis

B HCG with immunodeficiency: IgA deficiency
AFP with immunodeficiency: AT

selective IgA deficiency
UPT +ve: due to heterophile reaction
peristently high B HCG

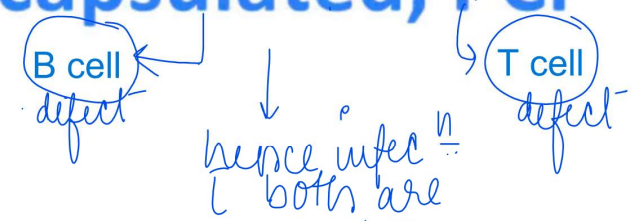
HYPER IGM SYNDROME

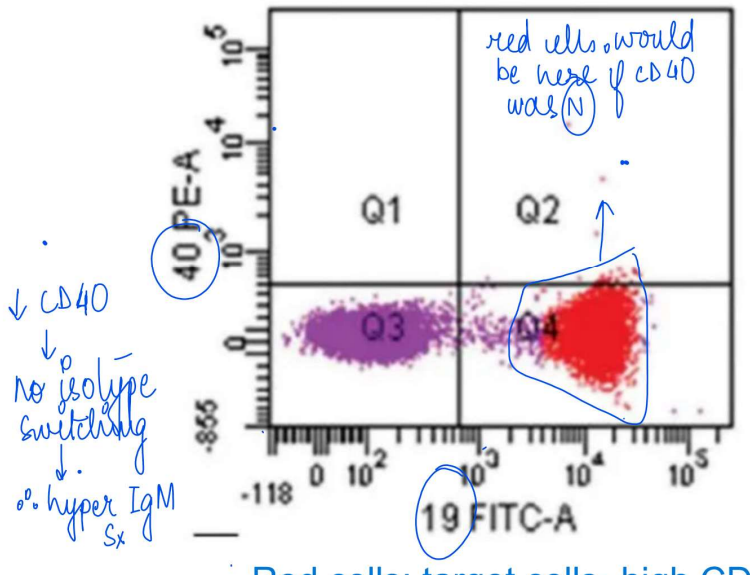
B, T cell normal

Low IgA, IgG, IgE AGE is low

AI hemolytic anemia

Encapsulated, PCP





↓ CD40 → no isotype switching → ∴ hyper IgM Sx

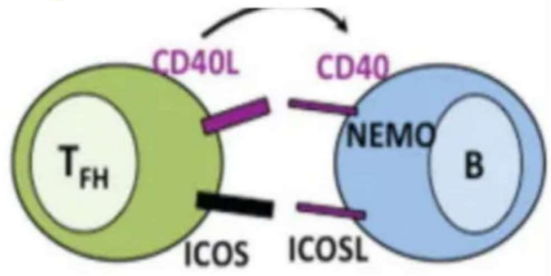
red cells would be here if CD40 was (N)

Red cells: target cells- high CD19, low CD40

(N) on all B cells, IgD & IgM are (↑) → native Igs → resp for switching → they become IgA, IgG, IgE = class switching

If no class switching, ↑↑ IgM.

class switching problem



CD40 and CD40L should ∘ interact for class switching

XLR (if CD40L ⊖)

T ulta- ⊞ so CD40L is on T cell

→ CD40 ⊖ ; AR

HYPER IGM syndrome

CD 154= CD40L

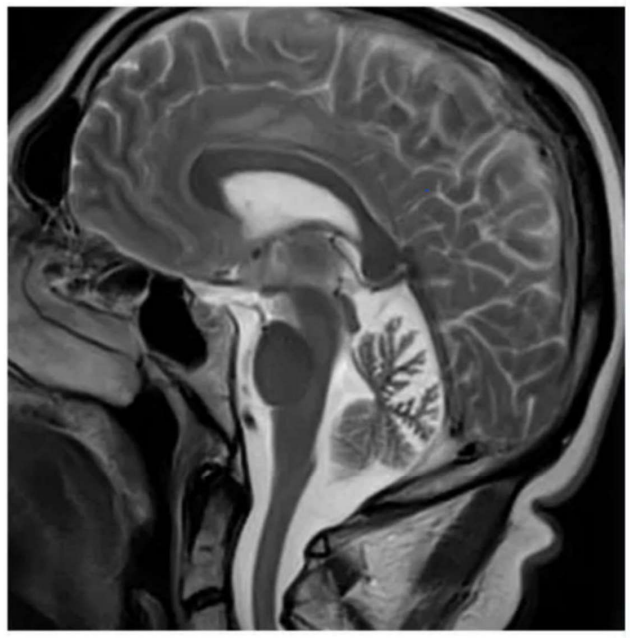
ATM

B+T cells
chr 11-also for MEN1
DNA repair affected
so photosensitivity
leukaemias, BRCA assocn

Raised AFP

Low IgA,G,E

AGE is low



cerebellar atrophy

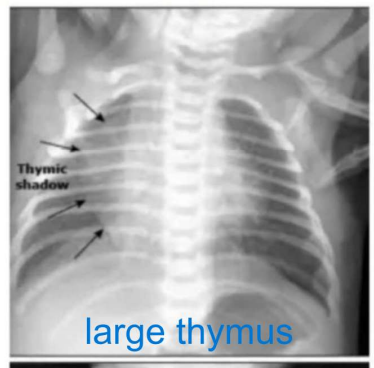
Low T-cell receptor excision circles

TREC

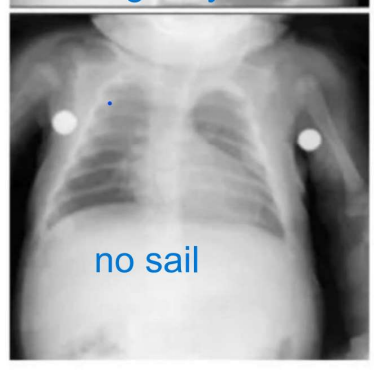
Birth

(LOW THYMIC FUNCTION)

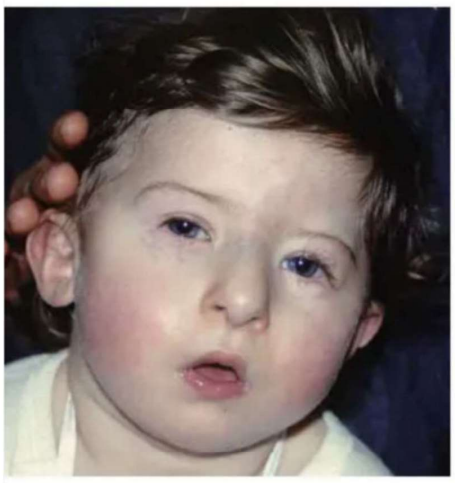
Thymic hypoplasia is not always diGeorge
no B cells no T cells
This is SCID
SCID types:
1. XLR: defect in Y subunit of cytokine receptor
2. AR: ADA deficiency
Gene therapy tried for first time here but not successful due to risk of leukaemia- T cell lymphomas
Rx: HSCT



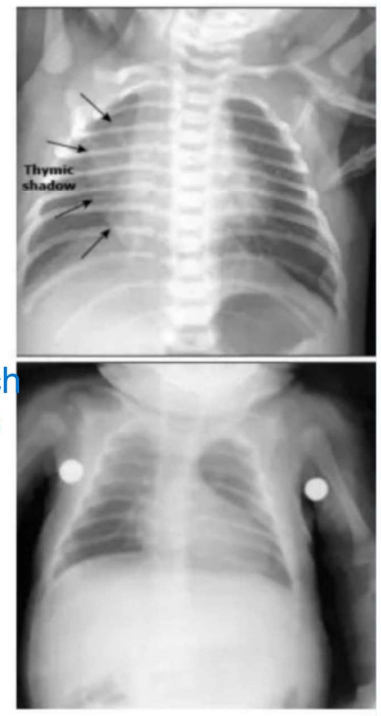
large thymus



no sail



DIGEORGE SYNDROME
absent thymus
no philtrum- also in fetal alc syndrome
CATCH 22
C- cleft lip and palate
A- abnormal facies
T- thymic hypoplasia
C- conotruncal septum
H- hypocalcemia- 3rd pouch and 4th pouch
22- 22q11 microdeletion- TBX1- regulates development of pharyngeal arches
IOC: FISH (for any microdeletion)
also wants job- autosomal dominant



Disseminated TB after BCG

TB has granuloma
IFN gamma
IL 12 receptor deficiency: body cannot fight TB

No urticaria

Dual screen:
PAPPA gave HP
HCG and PAPPA

Down's → HAE
H- hCG high
A- AFP
E- UEs

DOC % Danazol

hereditary angiedema

edema: Quincke's (laryngeal)

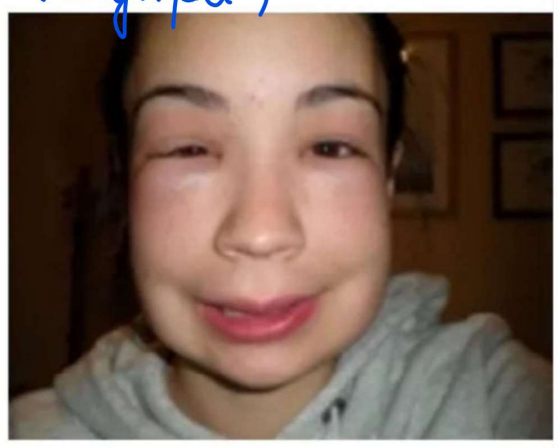


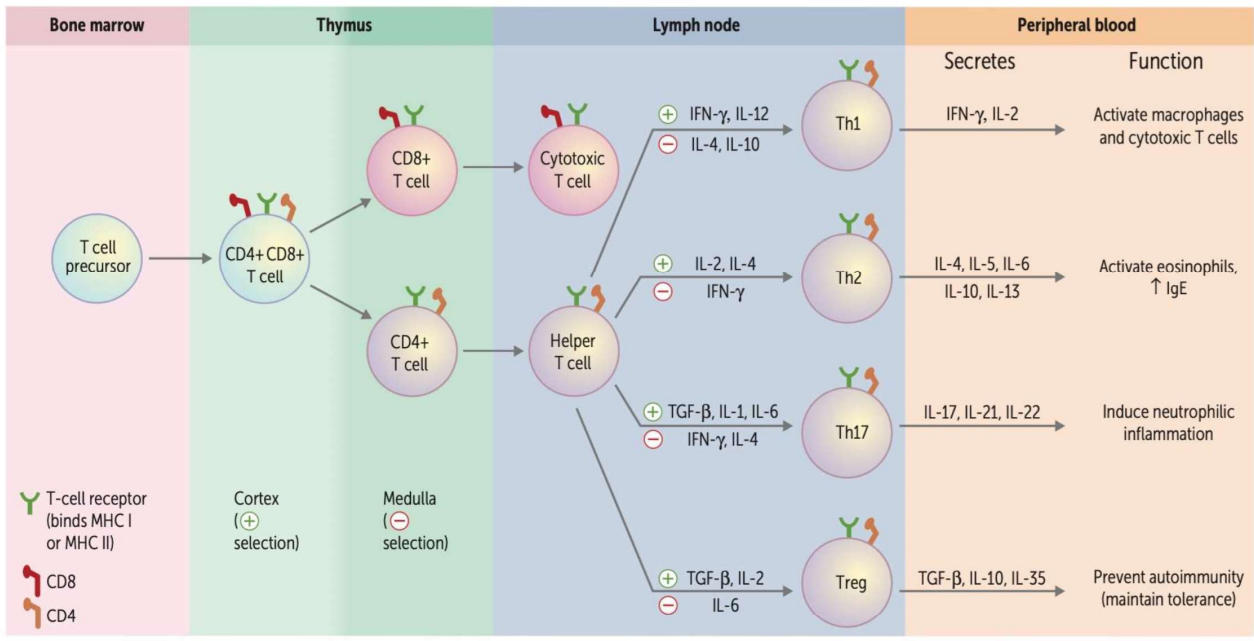
Table 1. Etiologies of hereditary angioedema syndromes

Type I HAE	Deficiency of C1INH ↓↓
Type II HAE	Defect in C1INH level (N), fun = ↓
Type III HAE	Normal C1INH; abnormal αFXIIa with gain-in-function mutations

Recurrent Neisseria infection

↳ terminal complement C5-C9 (MAC) deficiency.

Disorder	Defect	Inheritance	Buzz words
Wiscott-Aldrich	WASP	XLR	T → thrombocytopenia I → immunodeficiency E → eczema → ↑↑ IgA, IgE
Hyper IgE-JOB	STAT → Th17	AD	F → face A → abscess T → teeth E → eczema
Chediak-Hegashi	LYST	AR	L → light M → microtubule defect N → neutrophil → neutropathy P → platelet → pancytopenia O → giant granules
CGD	NADPH oxidase	XLR AR	C → catalase (+) G → granulomas D → DHR
LAD 1	Integrin → CD18	AR	L → late detachment A → absent pus D → dysfn° neutrophil
Bruton's agammaglobulinemia (BCELL)	Btx	XLR	• after 6 months • (−) germinal centres
CVID (BCELL)	BAFF / ICOS	AR / sporadic	• Teenage • Hyperplastic germinal centres
IgA deficiency (BCELL)	IgA , ? BAFF	sporadic	• URT (+) • anaphylaxis
Hyper IgM	CD40L → XLR CD40 → AR		
ATM	ATM (chr 11)	AR	↑↑ AFP
SCID (thymic hypoplasia =)	γ cytokine → XLR ADA → AR		
DiGeorge (thymic hypoplasia =)	TBX1 (microdel° 22q11)	AD	CATCH 22



Positive selection Thymic cortex. Double-positive (CD4+/CD8+) T cells expressing TCRs capable of binding self-MHC on cortical epithelial cells survive.

Negative selection Thymic medulla. T cells expressing TCRs with high affinity for self antigens undergo apoptosis or become regulatory T cells. Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (AIRE); deficiency leads to autoimmune polyendocrine syndrome-1 (Chronic mucocutaneous candidiasis, Hypoparathyroidism, Adrenal insufficiency, Recurrent *Candida* infections). "Without AIRE, your body will CHAR".

AUTOANTIBODY	
Anti-postsynaptic ACh receptor	Myaesthenia gravis
Anti-presynaptic voltage-gated calcium channel	Lambert Eaton MS
Anti-β_2 glycoprotein I	APLA
Antinuclear (ANA)	→ entry criteria for SLE
Anticardiolipin, lupus anticoagulant	→ SLE/APLA
Anti-dsDNA, anti-Smith	→ sp for SLE → ↑ flares
Antihistone	→ drug induced lupus
Anti-U1 RNP (ribonucleoprotein)	→ mixed CTD
Rheumatoid factor (IgM antibody against IgG Fc region), anti-cyclic citrullinated peptide (anti-CCP, more specific)	→ RA
Anti-Ro/SSA, anti-La/SSB	→ Sjogren
Anti-Scl-70 (anti-DNA topoisomerase I)	systemic sclerosis
Anticentromere	CREST (localised scleroderma)
Antisynthetase (eg, anti-Jo-1), anti-SRP, anti-helicase (anti-Mi-2)	Dermatomyositis
Antimitochondrial	→ PBC
Anti-smooth muscle, anti-liver/kidney microsomal-1	→ AI hepatitis
Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)/perinuclear ANCA (p-ANCA)	→ UC / MPA / Churg Strauss
PR3-ANCA/cytoplasmic ANCA (c-ANCA)	→ Wegener's
Anti-phospholipase A_2 receptor	→ membranous

↳ mouse model → Heyman's antigen

(weakness at rest)

cong. ♡ block in SLE (child)

now under antisynthetase syn

Anti-hemidesmosome	B.P
Anti-desmoglein (anti-desmosome)	Pemphigus
Antithyroglobulin, antithyroid peroxidase (antimicrosomal)	Hashimoto
Anti-TSH receptor	/ LATS → Graves' (long acting thyroid stimulator)
IgA anti-endomysial, IgA anti-tissue transglutaminase, IgA and IgG deamidated gliadin peptide	CD
Anti-glutamic acid decarboxylase, islet cell cytoplasmic antibodies	type 1 DM / 1.5 DM (LADA)
Antiparietal cell, anti-intrinsic factor	Pernicious
Anti-glomerular basement membrane	Goodpasture's

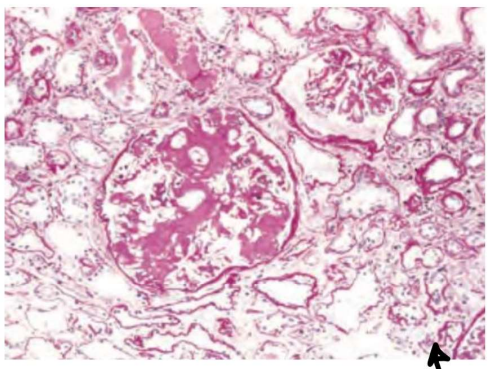
Cell surface proteins	
T cells	TCR (binds antigen-MHC complex), CD3 (associated with TCR for signal transduction), CD28 (binds B7 on APC)
Helper T cells	CD4, CD40L, CXCR4/CCR5 (coreceptors for HIV)
Cytotoxic T cells	CD8
Regulatory T cells	CD4, CD25
B cells	Ig (binds antigen), CD19, CD20, CD21 (receptor for Epstein-Barr virus), CD40, MHC II, B7 (CD80/86)
NK cells	CD16 (binds Fc of IgG), CD56 (suggestive marker for NK cells)
Macrophages	CD14 (receptor for PAMPs [eg, LPS]), CD40, CCR5, MHC II, B7, Fc and C3b receptors (enhanced phagocytosis)
Hematopoietic stem cells	CD34

unacademy

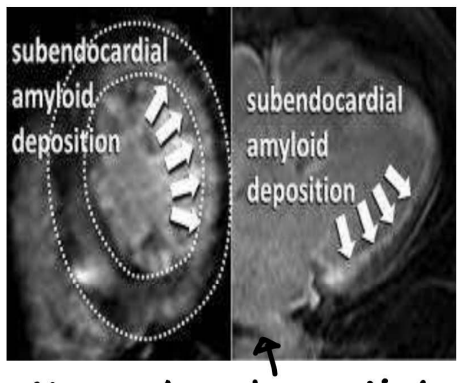
AMYLOIDOSIS → Abnormally folded β pleated proteins, resistant to proteases.

pressure atrophy of surrounding organs

COMMON TYPES	FIBRIL PROTEIN
Systemic	
Primary amyloidosis	AL . MC light chain - Lambda → Multiple myeloma ⊕ MC organ : kidney most specific organ : Heart
Secondary amyloidosis	AA . ⊕ IL1/6 chronic inflam. → RA, TB, RCC, Hodgkins lymphoma, Familial mediterranean fever → ↑IL1. ⊖ chronic bronchitis
Dialysis-related amyloidosis	$A\beta_2$ microglobulin → joints carpal tunnel syndrome
Localized	
Alzheimer disease	Aβ → brain . From APP on ch.21 → ↑r/o Alzheimers in Downs syndrome
Type 2 diabetes mellitus	IAPP [Islet asso. polypeptide]
Medullary thyroid cancer	A + calcitonin
Isolated atrial amyloidosis	ANP [Amyloid natriuretic peptide]
Systemic senile (age-related) amyloidosis	Wild ATTR (normal) → Heart
Familial amyloid polyneuropathies	Mutated ATTR → Nerves



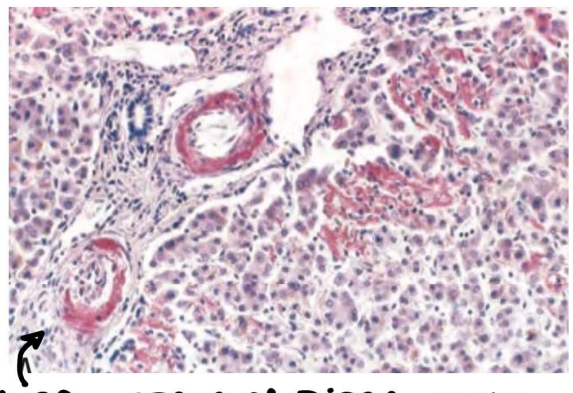
MC organ - Kidney
Nephrotic syndrome
Mesangium - 1st involved
Enlarges initially → shrinks



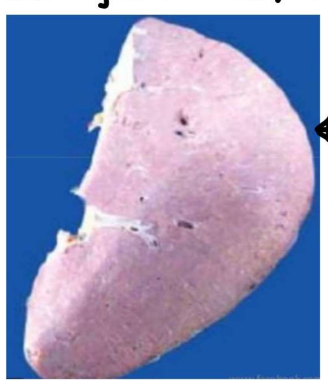
AL → subendocardial deposition. IOC - MRI

↙ Restrictive cardiomyopathy

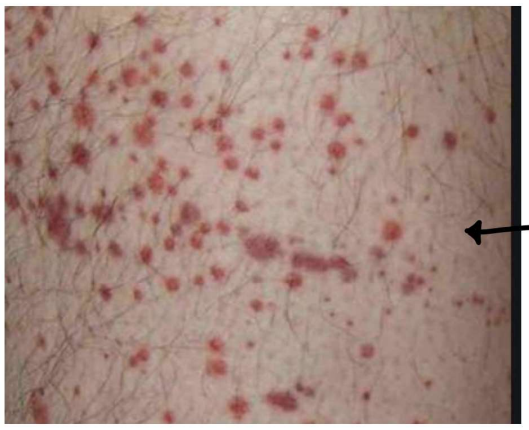
↘ Arrythmias



Liver - space of Disse → Ito & stellate cells for vit. A ⊕



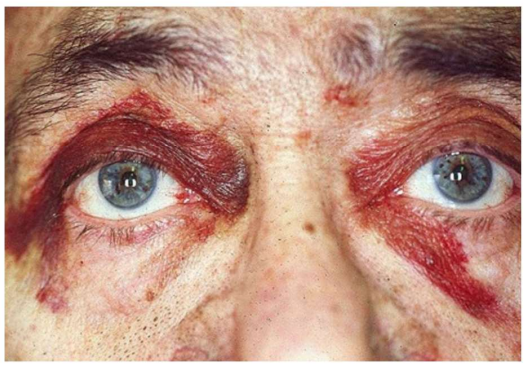
White pulp - sago spleen
Red pulp - lardaceous spleen.



Blood vessel subendothelial deposits → weak

← pinch purpura

carpal tunnel → syndrome ⊽ phalen sign. A/W dialysis AB_2 microglobulin.



← Racoon eyes

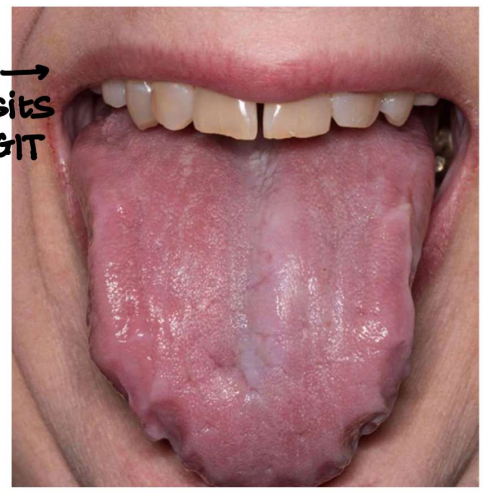
Amyloidosis

base of skull

Neuroblastoma

Macroglossia →

nodular deposits throughout GIT



DIAGNOSIS:

Sample: Abdominal fat aspirate> Rectal mucosal biopsy

MACROSCOPIC

- Waxy appearance → gross
- Lugols iodine staining → mahogany brown colour [same as oncocytoma]
- Adding H_2SO_4 to Lugols iodine → blue colour

MICROSCOPIC

Specific:

Congo Red → LM - pink; polarising light: apple green birefringens

Methy violet, crystal violet — Metachromatic dyes

Thioflavin T/S → Fluorescent green (uv)

Non-specific:

Toluidine blue

Alcian blue

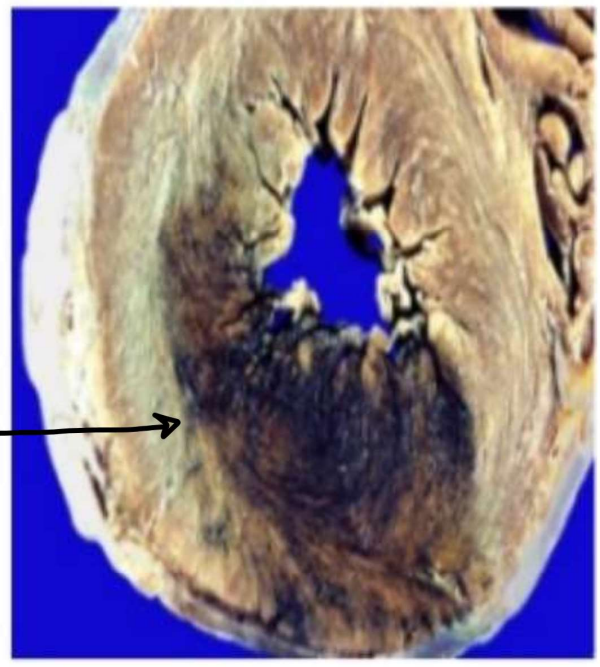
PAS ⊕

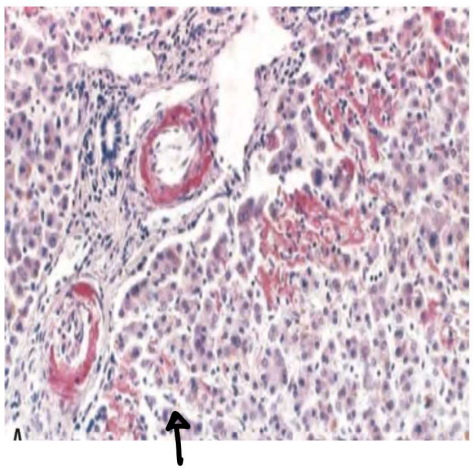
Electron microscopy

7.5-10nm, non-branching, fibrils → diameter Never ending length

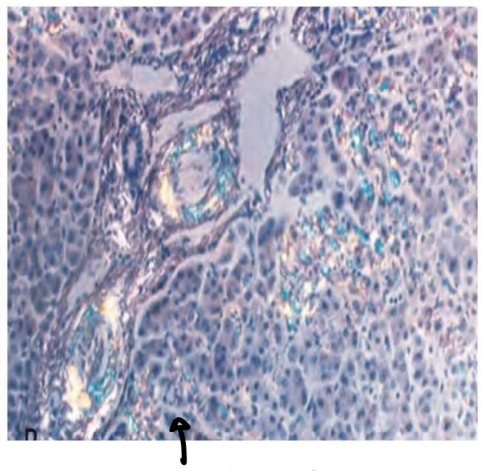
B-pleated structure → Xray crystallography & IR spectroscopy

1. **Stain on Gross**- oldest method used by Virchow on cut section of gross specimen is **Lugols Iodine** which imparts **mahogany brown** colour to the amyloid deposit which on addition of sulfuric acid turns **blue.**

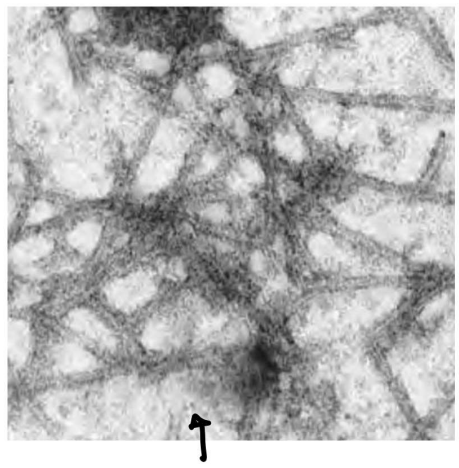




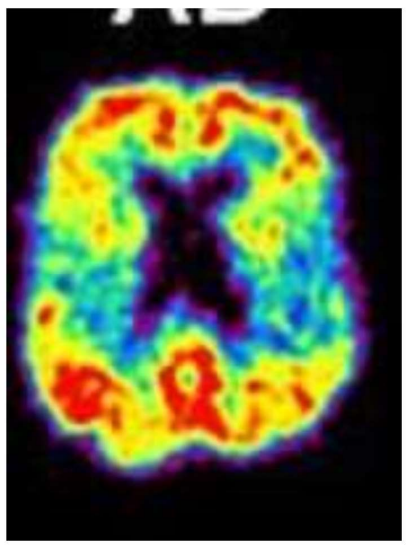
Congo Red - Light microscopy : pink amorphous



polarising light microscopy: Apple green birefringens



Electron microscopy

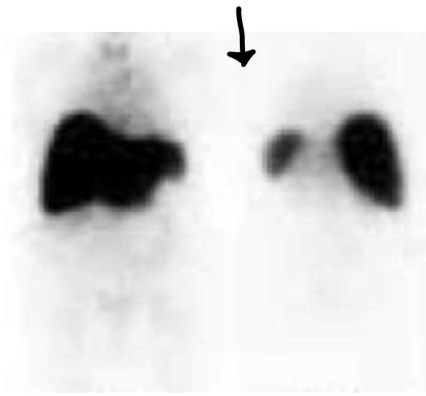


← Pitsburg compound B SPECT:

Aβ deposition Alzheimers

serum amyloid P [SAP] scintigraphy

very useful for the disease extent



AMYLOID INHIBITS COAGULATION FACTOR?

Factor 10
Pinch purpura ⊕