BLHD WEEK 2

HEMATOLOGY & IMMUNOLOGY

viruses
hypersensitivity
immunodeficiency

this week:
- AT T cells II & III
- AT Intro to Virology
- AT T cells II
- AT Immunosuppressants
- AT CSL: Eye
- AT CSL: informed consent
- TV HIV I
- TV HIV II
- TV Herpes I
- TV Herpes II
- AT Hypersensitivity
- TV Anatomy: Lymph System
- TV Histology: Thymus/Spleen/LN
- AT Lymph Node Disorders
- AT Primary Immunodeficiency

(SKETCHY TIME!)

VIROLOGY

OBLIGATE INTRACELLULAR PATHOGEN

am I alive?

ultimate goal: understand classification system

- ✓ RNA vs DNA
  - utilize host cell machinery (RNA pol II, translational machinery)
  - (+) strand: can utilize host cell machinery; can be translated directly; require RNA-dependent polymerases to replicate genome
  - (−) strand: must have virion RNA-dependent RNA polymerases to produce mRNA!; must make a positive strand to be translated
- ✓ single stranded vs double stranded
  - RNA: must have virion RNA-dependent RNA polymerases to produce mRNA!; segmented genome
  - DNA
- ✓ naked vs enveloped (LIPID)
- ✓ capsid shape/symmetry
  - helical
  - icosahedral
  - complex
- ? WHAT IS A RETROVIRUS & WHAT important virus follows this MOA?

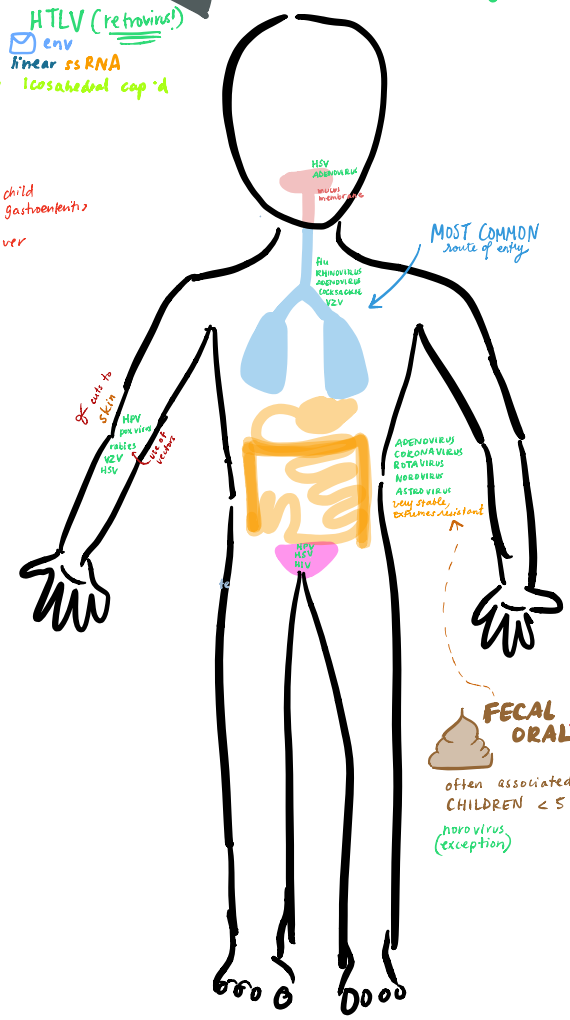
ONE CLASSIFICATION TYPE: by function

FUNCTION

- Hemorrhagic (blood bursting)
  - Dengue
  - Ebola
  - Lassa
- oncogenic (cancer causing)
  - Epstein Barr (EBV aka HHV-4)
  - papilloma
  - Hepatitis B + Hep C
  - Hepatitis C
  - HHV-8
  - HTLV-1
  - HTLV-2
- AIDS opportunistic
  - HIV-1
  - HIV-2
  - CMV (HHV-5)
- HHV herpes family
  - HSV 1 aka HHV-1
  - HSV 2 aka HHV-2
  - VZV aka HHV-3
  - Epstein Barr (EBV aka HHV-4)
  - CMV (HHV-5)
  - HHV-6
  - HHV-7
  - HHV-8

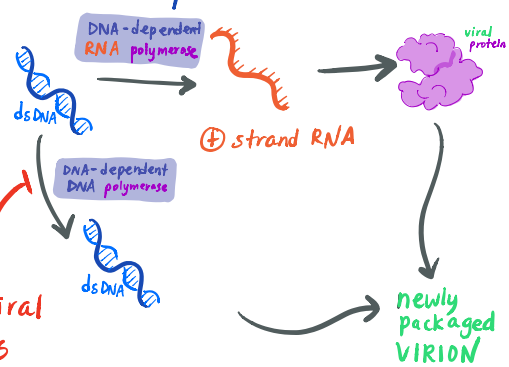
ONE CLASSIFICATION TYPE: by Routes of ENTRY

HTLV (retrovirus)
- env
- linear ss RNA
- icosahedral cap'd

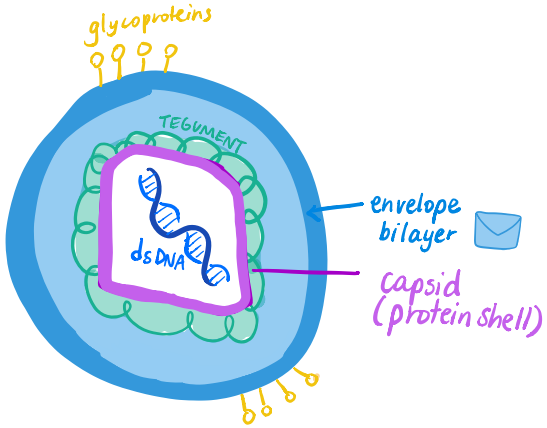


child gastroenteritis

ONE CLASSIFICATION TYPE: by VIRAL GENOMIC replication



will not work if virus is LATENT
e.g. VZV, reactivation



ONE CLASSIFICATION TYPE: by VIRUS STRUCTURE

DNA

RETRO VIRUS

single stranded
- parvovirus B19
- circovirus

double stranded

CAPSID?

CAPSID +

ICOSAHEDRAL

NAKED
- LINEAR
- CIRCULAR

ENVELOPED
- LINEAR
- CIRCULAR

CAPSID +

COMPLEX
- baculovirus

HELICAL
- small pox
- monkeypox
- vaccinia

RNA

RETRO VIRUS
- human immunodeficiency virus (HIV)
- human T-lymphotropic virus (HTLV1) (HTLV2)

single stranded

CAPSID?

CAPSID +

SHAPE

ICOSAHEDRAL

NAKED
- CALICIVIRUS
  - norovirus

ENVELOPED
- FLAVIVIRUS
  - dengue virus
  - zika virus
  - west nile virus
  - hepatitis C

HELICAL

ENVELOPED
- CORONAVIRUS
  - SARS
  - MERS

NO CAPSID

HELICAL

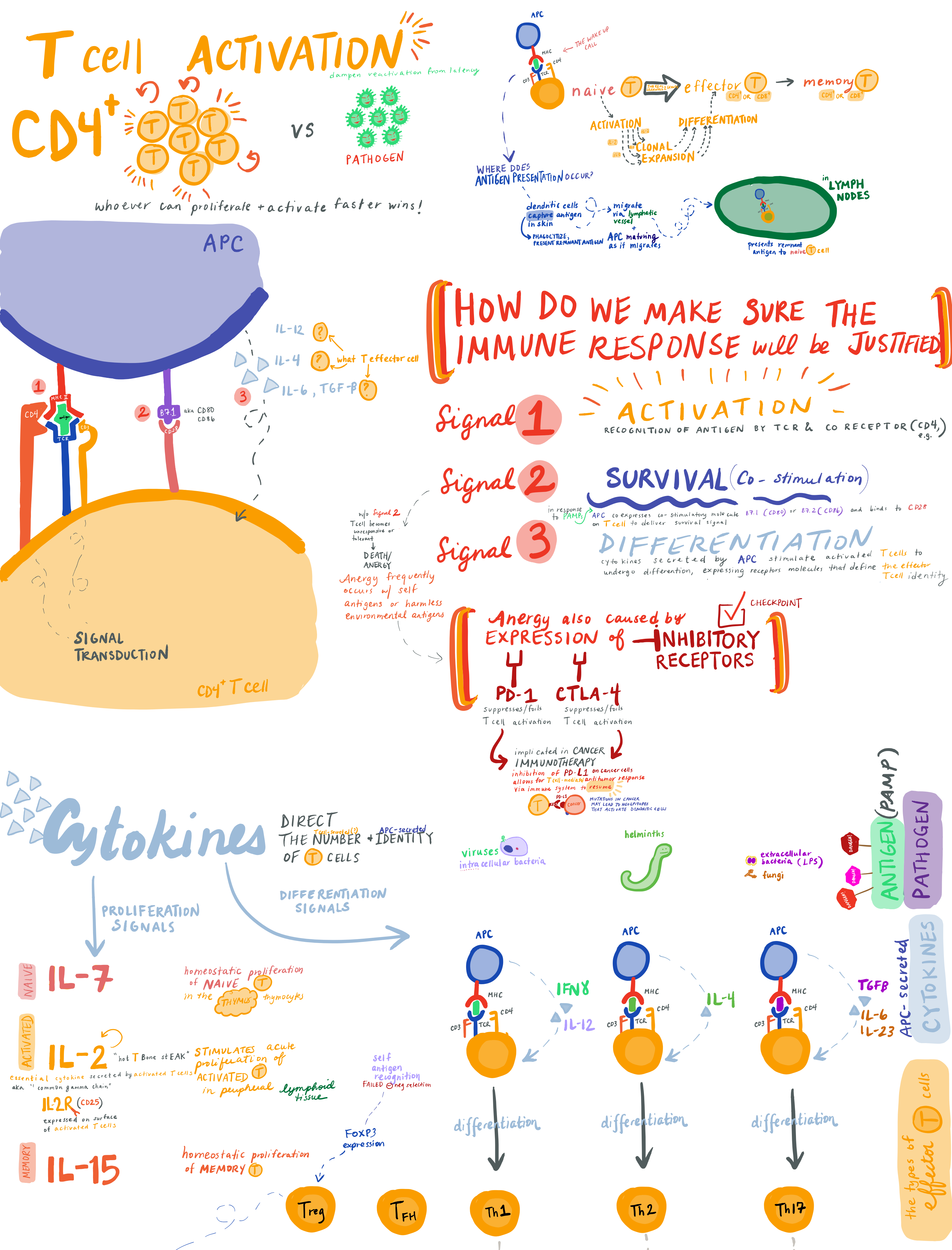
ENVELOPED
- BUNYAVIRUS
  - hantavirus
- FILAVIRUS
  - ebolavirus
- RHABDOVIRUS
  - rabies
- ARENAVIRUS
  - lassa virus
  - lymphocytic choriomeningitis virus (LCMV)
- ORTHOMXYOVIRUS
  - influenza virus
- PARAMXYOVIRUS
  - metapneumovirus
  - measles
  - mumps
  - respiratory synctial virus (RSV)
  - parainfluenza virus PIV-1
  - parainfluenza virus PIV-2
  - parainfluenza virus PIV-3
  - parainfluenza virus PIV-4

double stranded
- rotavirus

- adeno virus
- human papilloma virus
- JC polyoma virus
- human herpes virus-1 (HSV1)
- human herpes virus-2 (HSV2)
- human herpes virus-3 (HSV3)
- human herpes virus-4 (HSV4)
- human herpes virus-5 (HSV5)
- human herpes virus-6 (HSV6)
- human herpes virus-7 (HSV7)
- human herpes virus-8 (HSV8)
- hepatitis B (hepadna-)

PICORNAVIRUS
- poliovirus
- hepatitis A
- rhinovirus
- hepatitis E

TOGAVIRUS
- rubella virus
- chikungunya



T cell ACTIVATION
CD4+ vs PATHOGEN
dampen reactivation from latency
whoever can proliferate + activate faster wins!
APC
MHC
CD4
CD3
TCR
THE WAKE UP CALL
naive
effector
memory
CD4+ OR CD8+
ACTIVATION
DIFFERENTIATION
CLONAL EXPANSION
WHERE DOES ANTIGEN PRESENTATION OCCUR?
dendritic cells capture antigen in skin
migrate via lymphatic vessel
PHAGOCYTIZE, PRESENT REMNANT ANTIGEN
APC maturing as it migrates
in LYMPH NODES
presents remnant antigen to naive T cell
APC
MHC II
antigen
TCR
CD4
CD3
B7.1 aka CD80 CD86
CD28
IL-12
IL-4
IL-6, TGF-β
what T effector cell
SIGNAL TRANSDUCTION
CD4+ T cell
HOW DO WE MAKE SURE THE IMMUNE RESPONSE will be JUSTIFIED
Signal 1 ACTIVATION
RECOGNITION OF ANTIGEN BY TCR & CO RECEPTOR (CD4, e.g.)
Signal 2 SURVIVAL (Co-stimulation)
in response to PAMPs
APC co expresses co-stimulatory molecule on T cell to deliver survival signal
B7.1 (CD80) or B7.2 (CD86) and binds to CD28
Signal 3 DIFFERENTIATION
cytokines secreted by APC stimulate activated T cells to undergo differentiation, expressing receptors molecules that define the effector T cell identity
w/o signal 2 T cell becomes unresponsive or tolerant
DEATH/ ANERGY
Anergy frequently occurs w/ self antigens or harmless environmental antigens
Anergy also caused by EXPRESSION of INHIBITORY RECEPTORS
CHECKPOINT
PD-1
suppresses/foils T cell activation
CTLA-4
suppresses/foils T cell activation
implicated in CANCER IMMUNOTHERAPY
inhibition of PD-L1 on cancer cells allows for T cell-mediated anti tumor response via immune system to resume
MUTATIONS IN CANCER MAY LEAD TO NEOEPITOPES THAT ACTIVATE DENDRITIC CELLS
Cytokines
DIRECT THE NUMBER + IDENTITY OF T CELLS
T cell-secreted
APC-secreted
PROLIFERATION SIGNALS
DIFFERENTIATION SIGNALS
NAIVE IL-7
homeostatic proliferation of NAIVE T in the THYMUS thymocytes
ACTIVATED IL-2
"hot T Bone stEAK"
STIMULATES acute proliferation of ACTIVATED T in peripheral lymphoid tissue
essential cytokine secreted by activated T cells
aka "common gamma chain"
IL2R (CD25)
expressed on surface of activated T cells
MEMORY IL-15
homeostatic proliferation of MEMORY T
self antigen recognition
FAILED neg selection
FoxP3 expression
viruses
intracellular bacteria
helminths
extracellular bacteria (LPS)
fungi
ANTIGEN (PAMP)
PATHOGEN
DANGER!
APC
MHC
CD4
CD3
TCR
IFNγ
IL-12
IL-4
TGFβ
IL-6
IL-23
APC-secreted CYTOKINES
differentiation
Treg
TFH
Th1
Th2
Th17
the types of effector T cells

Treg

IL-10
TGF-β
attenuate immune respons
activates M2 macrophage

T_{FH}

located in germinal centers
aid in helping B cells perfect their antibodies against foreign pathogens

Th1

IFN-γ
activates macrophages
CHRONIC ACTIVATION → GRANULOMAS
encourages B cell class switching → the right Antibody Y → IgG
increased MHC
costimulator expression
secretion of cytokines + chemokines: TNF, IL-1, IL-12

PJP
mycobacterium tuberculosis

Th2

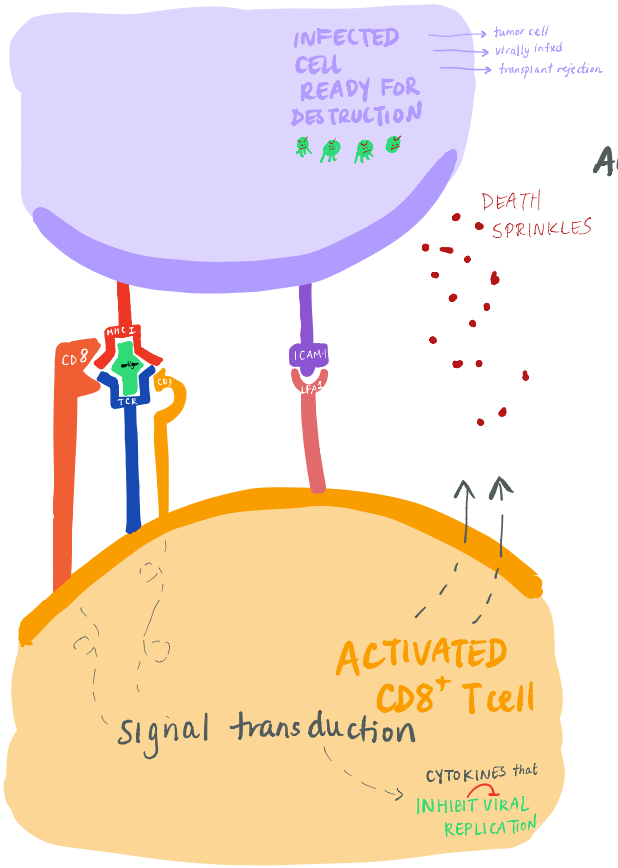
IL-4
@ germinal center encourages B cell class switching to form IgE Y
IgE → mast cells → degranulation → HISTAMINE: VASOACTIVE SUBSTANCES

IL-5
activates eosinophils

Th17

IL-17
attracts neutrophils + macrophages to site of infxn
skin + mucosa
autoimmune dz (psoriasis)

CD8+



what do ACTIVATED CD8+ cells look like?

also occurring in LYMPH NODE

ACTIVATED CD8+ cytotoxic T cells express + release

perforin — permits entry

granzymes — activates APOPTOSIS

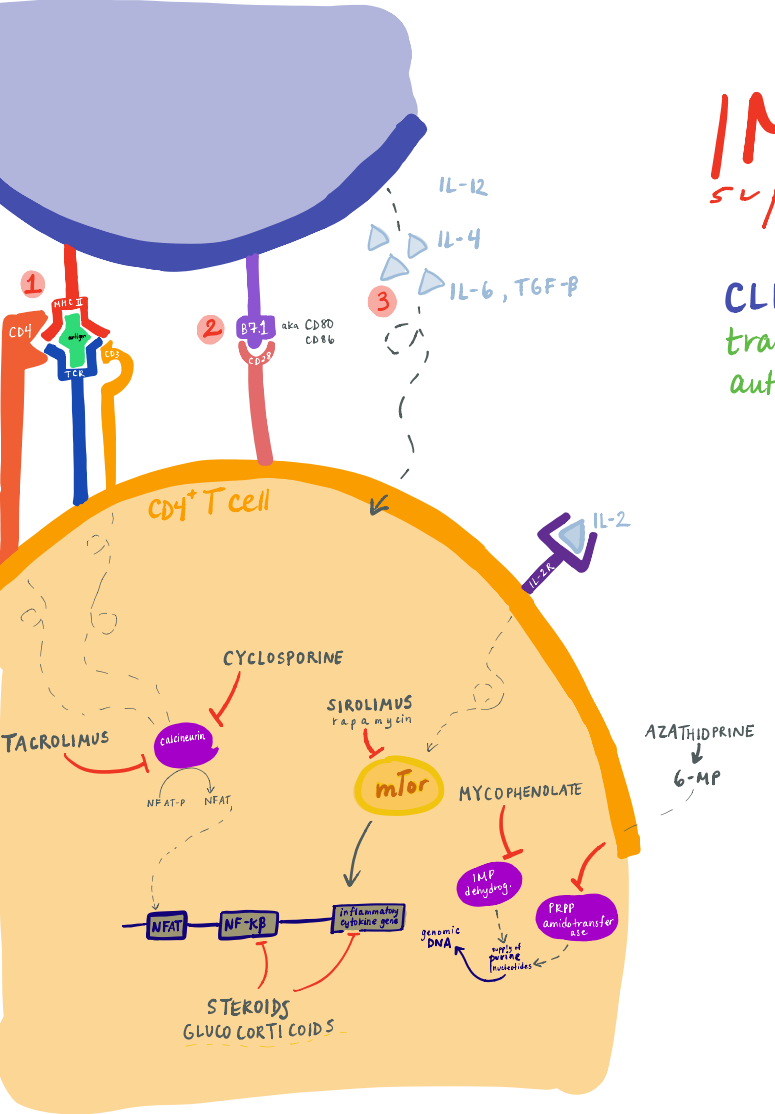
CYTOLYTIC activity → APOPTOSIS

IMMUNOsuppressants

drugs that dampen the IMMUNE SYSTEM

CLINICAL USES
transplant rejection
autoimmune diseases

GENERAL ADVERSE EFFECTS
↑ incr risk of infection
↑ incr risk of malignancy



(VIRUS vs HOST CELL)
GRAFT vs HOST

due to MHC mismatch: Recipient immune system DESTROYS MHC of disparate graft

? what type of effector T cell most implicated in GvHD?

MONOCLONAL Antibodies

rituximab ∝CD20
TX: B-cell non Hodgkins lymphoma, chronic lymphocytic leukemia CLL, idiopathic thrombocytopenic purpura ITP

alemtuzumab ∝CD52
TX: chronic lymphocytic leukemia CLL, multiple sclerosis MS

CALCINEURIN INHIBITORS

cyclosporine CYP3A4
TX: immunosuppression
ADR: nephrotox, hypertension (HTN), hirsutism, gingival hyperplasia

tacrolimus (FK506) CYP3A4
TX: immunosuppression
ADR: nephrotox, hypertension (HTN), hyperglycemia, allopecia, neurotox

ANTI PURINES

azathioprine ⊣ salvage pathway, ⊣ de novo purine synth
TX: immunosuppression
ADR: pancytopenia, n/v, (alopecia, hepatotox, pancreatitis rare)
DO NOT USE w/ ALLOPURINOL → gout

mycophenolate ⊣ de novo purine synth
TX: immunosuppression
ADR: nausea, vom, diarrhea (n/v/d), GI issues, CMV susceptibility

mTOR1/mTOR2 INHIBITORS
inhibits T cell response to IL-2

sirolimus CYP3A4
TX: immunosuppression
ADR: pancytopenia, hypercholesterolemia, high TG, mouth ulcers, HTN

mTorc2 mTorc1 ? WHAT PATHWAY INVOLVES THESE TWO PROTEIN COMPLEXES?

PRIMARY ~~adaptive~~ IMMUNODEFICIENCIES

missing parts of the immune system d/t congenital, genetic defects

no B → no Ab ↴

polysaccharide coat: ENCAPSULATED — HELPS BUGS EVADE PHAGOCYTOSIS / COMPLEMENT
- Neisseria
- Haemophilus influenza
- Strep pneumoniae

B cell ONLY

• X-linked Agammaglobulinemia

mutation or deficiency of **BTK** (XLR)

no B cells
no antibodies of any isotype
flow cytometry to diagnosis

LABS	
IgM	Ø NONE
IgG	Ø NONE
IgA	Ø NONE
IgE	Ø NONE
WBC	LOW
Hgb	--
Platelet	
ABS # Neutr.	--
ABS # Lymphocyte	LOW
ABS # Monocyte	--
ABS # Eosinophil	--
$CD3^+$	--
$CD3^+$ $CD4^+$	--
$CD3^+$ $CD8^+$	--
$CD3^-$ $CD16^-$ $CD56^+$	--
$CD19^+$	NONE

tx: IVIG

• Selective IgA deficiency

★ MOST COMMON 1° immunodeficiency

GI infxns
Respiratory infxns } IgA in mucosal linings
may have anaphylaxis to blood products w/ IgA... forms ANTIBODIES

LABS	
IgM	--
IgG	--
IgA	LOW
IgE	--
WBC	HIGH
Hgb	--
Platelet	--
ABS # Neutr.	HIGH
ABS # Lymphocyte	--
ABS # Monocyte	--
ABS # Eosinophil	--
$CD3^+$	--
$CD3^+$ $CD4^+$	--
$CD3^+$ $CD8^+$	--
$CD3^-$ $CD16^-$ $CD56^+$	--
$CD19^+$	--

tx: IVIG (?)
+ supportive care

• Common Variable Immunodeficiency

recurrent sinopulm. infections (encapsulated)
poor vaccine response
risk of autoimmune disorders ITP AIHA

LABS	
IgM	LOW
IgG	LOW
IgA	LOW
IgE	--
WBC	HIGH
Hgb	LOW
Platelet	LOW
ABS # Neutr.	--
ABS # Lymphocyte	--
ABS # Monocyte	--
ABS # Eosinophil	--
$CD3^+$	--
$CD3^+$ $CD4^+$	--
$CD3^+$ $CD8^+$	--
$CD3^-$ $CD16^-$ $CD56^+$	--
$CD19^+$	LOW*

*low memory B cells

tx: IVIG

T cell ONLY

• Di george Syndrome

22q11.2 deletion

Failure of 3rd + 4th pharyngeal pouch developm.
abnormal thymic developm.
hypoparathyroidism LOW CALCIUM
cardiac defects (structural)
TETRALOGY of FALLOT
TRUNCUS ARTERIOSUS
VENTRICULAR SEPTAL DEFECT

LABS	
IgM	--
IgG	--
IgA	--
IgE	--
WBC	
Hgb	--*
Platelet	
ABS # Neutr.	--
ABS # Lymphocyte	--
ABS # Monocyte	--
ABS # Eosinophil	--
$CD3^+$	LOW
$CD3^+$ $CD4^+$	LOW
$CD3^+$ $CD8^+$	LOW
$CD3^-$ $CD16^-$ $CD56^+$	--
$CD19^+$	--

+ LOW CALCIUM

tx: calcium
cardiac tx
thymus transplant

• Job's / Hyper IgE

STAT3 GAIN OF FXN

Th17 cell deficiency → impaired recruitment of neutrophils
coarse facies
skin infxns S. aureus
pneumonia
bone fractures
retention of baby teeth
eczema (eosinophil, IgE)

tx: supportive care

LABS	
IgM	--
IgG	--
IgA	--
IgE	HIGH
WBC	--
Hgb	--
Platelet	--
ABS # Neutr.	--
ABS # Lymphocyte	low?
ABS # Monocyte	--
ABS # Eosinophil	HIGH
$CD3^+$	
$CD3^+$ $CD4^+$	LOW*
$CD3^+$ $CD8^+$	--
$CD3^-$ $CD16^-$ $CD56^+$	--
$CD19^+$	--

*Th17 cell deficiency

• Chronic Mucocutaneous Candidiasis

CLASS OF DISORDERS

mutation or deficiency of **AIRE** ······> APECED
autoimmune polyendocrinopathy candidiasis ectodermal dystrophy... phew!

defect in negative selection of T cells in thymus
autoreactive T cells in periphery
nail dystrophy
alopecia

B & T combined

Severe Combined Immunodeficiency (SCID)

mutation or deficiency of **ADA** (AR) or **RAG1/2** (AR) or **IL-7Rα** (AR) or **CD3** (AR) or **JAK3** (AR) or **IL2RG** (XLR) gamma chain defect, most common

Failure to thrive ···> FATAL if untreated
diarrhea
persistent severe infections B/V/F
Fam Hx: early childhood death

also can have ABSENT THYMIC SHADOW

LABS	
IgM	--
IgG	--
IgA	--
IgE	--
WBC	LOW
Hgb	
Platelet	--
ABS # Neutr.	--
ABS # Lymphocyte	LOW
ABS # Monocyte	--
ABS # Eosinophil	--
$CD3^+$	LOW!!
$CD3^+$ $CD4^+$	LOW!!
$CD3^+$ $CD8^+$	LOW!!
$CD3^-$ $CD16^-$ $CD56^+$	LOW!!
$CD19^+$	LOW*

low TREC ⇝ low thymic output

tx: Bone marrow transplant
IVIG if indicated
prophylaxis for PJP, fungal
AVOID breast feeding if mom CMV^+
ADA enzyme if indicated
gene therapy ...!?

Hyper IgM

failure of B cell class switching + T cell activation

mutation or deficiency of **CD40L**

opportunistic infxns
sinopulmonary bacterial infxns
viral infxns
fungal infxns PJP, cryptosporidium

LABS	
IgM	HIGH
IgG	LOW
IgA	LOW
IgE	LOW
WBC	LOW
Hgb	
Platelet	--
ABS # Neutr.	--
ABS # Lymphocyte	--
ABS # Monocyte	--
ABS # Eosinophil	--
$CD3^+$	--
$CD3^+$ $CD4^+$	--
$CD3^+$ $CD8^+$	--
$CD3^-$ $CD16^-$ $CD56^+$	--
$CD19^+$	--

($CD3^+$, $CD3^+$ $CD4^+$, $CD3^+$ $CD8^+$: impaired fxn; $CD19^+$: impaired fxn)

tx: Bone marrow transplant

Wiskott-Aldrich – ACTIN

mutation or deficiency of **WAS** — actin polym

eczema, petechiae,
bacterial infxns
viral infxns
fungal infxns

thrombotic thrombocytopenic purpura

tx: Bone marrow transplant
IVIG

LABS	
IgM	LOW
IgG	LOW
IgA	--
IgE	--
WBC	
Hgb	
Platelet	LOW!!
ABS # Neutr.	
ABS # Lymphocyte	--
ABS # Monocyte	--
ABS # Eosinophil	--
$CD3^+$	LOW
$CD3^+$ $CD4^+$	LOW
$CD3^+$ $CD8^+$	LOW
$CD3^-$ $CD16^-$ $CD56^+$	--
$CD19^+$	--

INNATE → Leukocyte Adhesion Deficiency

mutation or deficiency of **LAD1**
CD18 integrin beta 2

affects migration of neutrophils
absence of neutrophils @ infxn sites... high in serum → leukocytosis (also seen in systemic corticosteroid use)
absence of pus formation
impaired wound healing
skin/mucosal infxns
delayed (>1 month) separation of umbilical cord

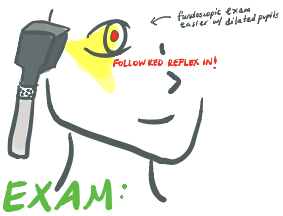
prophylaxis antibiotix
tx: Bone marrow transplant

LABS	
IgM	--
IgG	--
IgA	--
IgE	--
WBC	HIGH
Hgb	--
Platelet	--
ABS # Neutr.	HIGH
ABS # Lymphocyte	--
ABS # Monocyte	--
ABS # Eosinophil	--
$CD3^+$	--
$CD3^+$ $CD4^+$	--
$CD3^+$ $CD8^+$	--
$CD3^-$ $CD16^-$ $CD56^+$	--
$CD19^+$	--

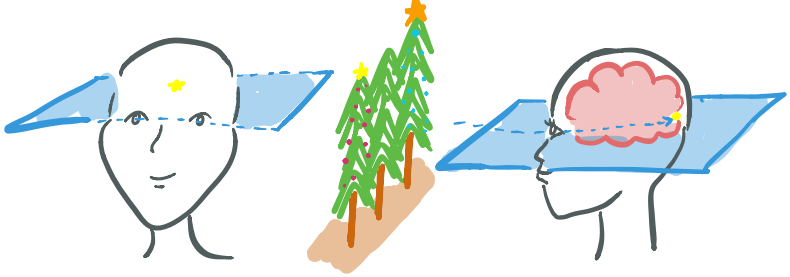
INNATE → Chediak Higashi – Microtubular dysfxn

CSL: THE EYE EXAM

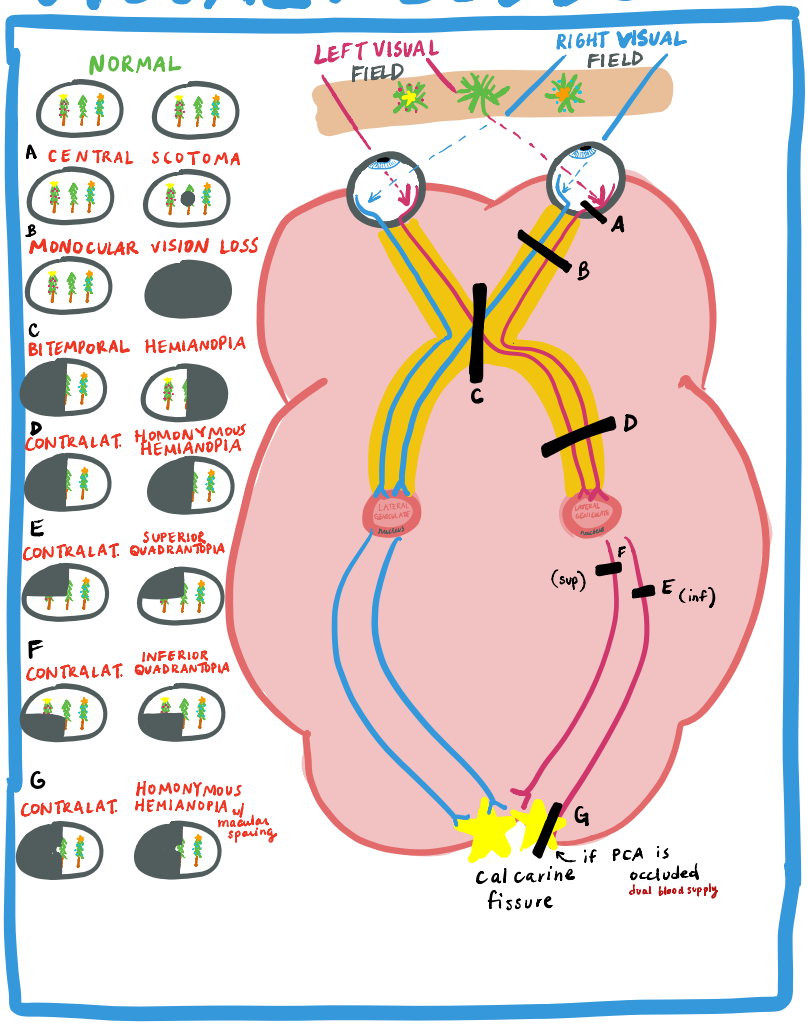
1) visual acuity
2) appearance of the lids, lashes, lacrimal gland, lymph nodes
   - pre auricular
   - submandibular
3) iris, conjunctiva, cornea, sclera
4) pupils
5) visual fields
6) extra ocular muscles of eye
7) fundoscopic examination



NORMAL FUNDOSCOPIC EXAM:



VISUAL FIELD DEFECT



Hypersensitivity

TYPE I
fast!!!

anaphylaxis, allergic reaction

food
bee sting
penicillin

ATOPIC: rxn to allergen occuring in a part of body not in contact w/ allergen

M.OA

IMMEDIATE: IgE, degranulation, mast cells, basophils → release of histamine

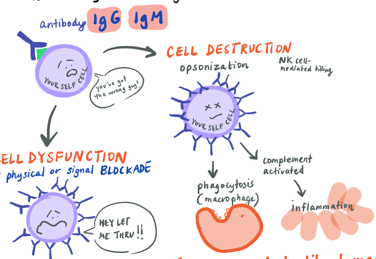
LATER: chemokines + cytokines → eosinophils; inflammation, tissue damage

CLINICAL CORRELATES

- ALLERGIC RHINITIS
- ALLERGIC ASTHMA → allergic bronchopulmonary aspergillosis
- ANAPHYLAXIS
- IgE-mediated FOOD ALLERGIES
- PENICILLIN RXN (IgE)

TYPE II
perfectly executed wrong target

antibody IgG IgM

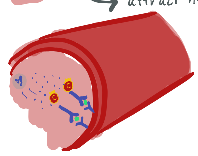


Rheumatic fever (α M protein looks like human antigen)

- BLHD HEMOLYTIC ANEMIA
- SBM MYESTHENIA GRAVIS
- CPR GOODPASTURE'S SYNDROME
- HODI GRAVES' DISEASE
- PENICILLIN - AIHA inducing
- II SYSTEMIC LUPUS ERYTHEMATOUS III (SLE)
- PERNICIOUS ANEMIA
- PEMPHIGUS VULGARIS
- HEPARIN INDUCED THROMBOCYTOPENIA
- HEMOLYTIC DISEASE OF NEWBORN

TYPE III
poorly executed back up on the vasculature highway

IMMUNE COMPLEX deposition
antigen - antibody - complement
IgG → attract neutrophils → LYSOSOMAL ENZYMES



- ARTHUS REACTION → tetanus (tDAP), insulin
- SERUM SICKNESS → rabies/tetanus α anti-toxin, penicillin, infliximab, rituximab
- VASCULITIDES → POLYARTERITIS NODOSA (← HepB), RPGN
- III HYPERSENSITIVITY PNEUMONITIS IV

TYPE IV
cell mediated
slow / delayed

CD4⁺ T cells → inflammatory-inducing cytokines

CD8⁺ T cells → kill targeted cells directly

- SARCOIDOSIS (CD4⁺) noncaseating
- GRANULOMATOUS D/2 (TB) caseating
- CONTACT DERMATITIS
- PSORIASIS
- CELIAC DISEASE
- DIABETES MELLITUS TYPE 1
- SJOGREN'S / SICCA
- MULTIPLE SCLEROSIS (myelin basic protein)
- INTERSTITIAL NEPHRITIS (penicillin)

DIAGNOSTIC TESTS

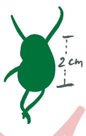
- SKIN PRICK TEST (fast)
- IMMUNOFLUORESCENT STAINING
- C1q BINDING ASSAY
- PATCH TEST
- PPD (TB) – WHY YOU HAVE TO RETURN TO JBT 48 hrs AFTER PPD TEST

Lymph NODE DISORDERS = adenopathies

what is lymph?
extracellular fluid from capillaries
distinct system from vascular system
drain & collect @ lymph nodes (LN) – site of filtration, removal of infxn organisms
drains into venous system @ right subclavian or thoracic duct → left subclavian

why do we care about identifying & defining lymph nodes by region?
what can it tell us?
- where pathology – cancer, infection originated
- guides surgery – proper resection means knowing which nodes to excise
- local vs systemic → benign (contained) vs. malignant (metastatic) – LYMPHOMA STAGING

>2 cm



CANCER: "constitutional" B symptoms – fever, night sweats, weight loss (unintentional); FIXED, FIRM LN

INFECTION: fever (acute); PAINFUL, TENDER, MOBILE

LYMPHEDEMA: swelling, discomfort, ↑ incr risk of infxn; DISRUPTED DRAINAGE d/t SURGERY

ENLARGED LN CHAINS: SYSTEMIC DISEASE – autoimmune, granulomatous

hydralazine + allopurinol