Intracellular pathogens 1

Immunity to Intracellular pathogens :

- recognized by TLR & NLR — phagocytes & Nk cells are main cells.

- intracellular bacteria activate Nk cell :
  1. induce expression of Nk-cell activating ligand (on infected cell)
  2. induce production of IL-12 + IL-15 which are Nk-activating cytokines.
     → produced by dendritic cells & macrophages.

* major mechanism against intracellular bacteria → T cell mediated immunity.

* Nk cells have → activating receptors (activate protein tyrosine kinase PTKs) → recognize infected cells
  → inhibiting receptors → recognise healthy cells.
  (recognise MHC I → healthy cells)
  (activate protine tyrosie phosphatase PTP)

* Nk can recognise cells without MHC I → recognition of missing self

* Nk have (Fc δ RIII)(CD16) receptors that recognize antibody-antigen complex.
  (activates)
  allows Nk to lyse cells through Antibody dependent cytotoxicity ADCC

* Nk in viral infection : - secretes IFNδ + TNFα
  IFNδ → activates macrophages
  TNFα → activates Nk tumor cell killing.

* L. Monocytogenes bacteria, phagocytosed by macrophages & may servive & escape into the cytoplasm.

* CD4+ respond to MHC II, produce IFN-δ → activate phagocytes.
  CD8+ respond to MHC I, direct kill the infected cell.

* innate immunity releases type 1 interferons in viral infections (early mediator)
  ① activate transription of protein can produce antiviral state in the cell
  genes confer on the cell a resistence to viral infections
  ② cause sequestration of lymphocytes in lymph nodes
  ③ increase cytotoxicity of NK + CD8+
  ④ upregulate expression of MHC-I

Intracellular pathogens 2

TH1 produce IFN-γ, TNF, chemokines & cytokines.
regulates macrophage activation by contact mediated signals by CD40L-CD40

* Adaptive immune response to microbes that live inside the phagosome is mediated by TH1 cells → IFN-γ → induce IgG
positive feedback

TH2 → mediate helminthic parasite infection + allergy i.e.
stimulate IgE by IL4 / activate eosinophils by IL-5 + IL-13
→ CD4+

TH17 → extracellular fungi & bacteria.
produce IL-17 → recruit leukocytes + neutrophils.

CD8+ → microbes that infect & replicate in the cytoplasm.
→ may cause tissue damage called: delayed-type hypersensitivity (DTH)

* Tcells need to proliferate & differentiate into memory & effector cells that require: - antigen recognition - costimulation - cytokines.
activation.

* Costimulatory pathway of T cells:

CD28 ~ B7-1 (CD80)
B7-2 (CD86)
on APCs

- T cell surface receptors
- includes inhibitory & activating receptors. → inhibitory receptors include: ① CTLA4 ② PD-1

* TNF stimulates migration of T cells (not naive)

* most important cytokine and first released by T cells is: IL-2
IL-2 stimulates survival, proliferation & differentiation of antigen-activated T cells (autocrine growth factor)

* CD8+ killer cells + NK → have granzymes + perforins

* T regulatory cells express: CD25, CD4, FOXP3
Mediators are inhibitory cytokines: IL-10, TGF-β, IL-35
① maintain tolerance, prevent autoimmunity & limit chronic inflammation
② limit beneficial respons by suppressing sterilizing immunity + limit anti-tumor immunity

* fungal infections: mycoses

VDJ recombination 1

* Antigen receptor gene rearrangements:

heavy chain.

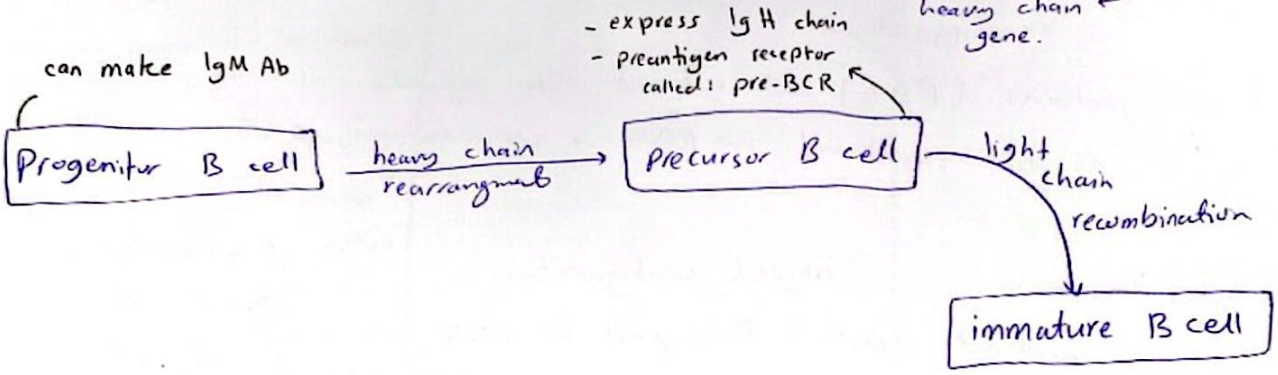
5'(V ——— D ——— J – Cγ)3'

heavy chain: 40 23 6

VDJ recombination.

① heavy chain rearrangement (~~Blast antigen receptor~~)

first antigen receptor chain to be rearranged is Ig H gene (heavy chain gene.)



* the heavy chain recombination: ① J & D recombination → bind each other bringing the C in close proximity.

② VDJ recombination → J, D will bind to V region bringing Cμ more close

* the whole VDJC is RNA rn (transcription)

③ splicing to remove the introns → mRNA

④ this mRNA will be translated to heavy chain.

IgM have 4 constant regions, rest heavy chain have 4

- kappa chain

* the light chain recombination: VJ recombination

↳ No D segment.

light chain.

5'(V ——— J – C_K)3'

38 5

- VJ then splicing then translation.

* there are hypervariable regions: Complementary-determining region

(HVR)s (CDRs)

there are 3 CDRs on both L & H chains. (7)(12 or 23)(9)

recombination signal sequence. consists of heptamer (7) separated by 12 or 23 base pairs from a nanomer (9)

(RSS)

VDJ recombination 2

* there are two ways to initiate the recombination:

(1) Deletion (2) Inversion

↳ (hairpin loop configuration)

* hairpin loop is formed where you can see V & J paralled to each other.

- & 12/23 are on the side can undergo recombination
- proteins (RAG) will cut of other segments allowing V&J to be recombined. → RNA → splicing → mRNA

(2) Inversion or Tangled configuration without deletion of any part of DNA.

12 + 12 X
23 + 23 X
12 + 23 ✓

Proteins involved:

(1) In kappa chain: RAG1, RAG2 will bind the motifs of RSS
- will bind each other forming hairpin loop
- will cleave RSS motifs

(2) ku70, ku80 will bind J & V segments.
↳ initiate repair by forming loop (hairpin)

(3) DNA protein kinase (Artemis) will open the loop formed by ku

(4) terminal deoxynucleotidyl transferase (TDT) will add nucleotides to the segments. J & V randomly.

(5) DNA ligase + XRCC4 will ligate the ends together. creating phosphodiester bonds.

Extracellular pathogens 1

✡ immunity against Extracellular microbes.

principle mechanisms :

① phagocytosis

phagocytes recognize bacteria that are bound to antibodies by Fc receptors.

- IgG1 + IgG3 → Fc receptors

phagocyte FcγRI receptor binds antibody coated particle leads to engulfment + phagocytosis.

call this increase production of:

phagocyte oxidase (respiratory burst)

inducable NO synthase (iNOS)

② inflammatory response

- hydrolytic enzymes (kill large pathogens)

③ Complement activation.

سيبكم انه فاضيين هون حسيتهم معلومات عامه ف ما كتبت😂

✡ antimicrobial peptides : - net positive charge (+) → cations.
get attracted to -ve charged

→ Defensins : small, produced by endothelial cells of mucosal surfaces & granule-containing leukocyte.

→ Cathelicidines : - produced by neutrophils & barrier epithelia

cleavage - cleaved to pose bactericidal & immunomodulatory functions.

✡ Primary ciliary dyskinesia → ① inherited ② impaired mucociliary clearance ③ lead to repeated chest infections.

hijacked by tumors to exert immunosupression effect.

✡ chemokines : include CC, CXC, CXCL8 (IL-8)

- induce chemotaxis (migration)
- induce phagocytosis.

all chemokines are cytokines but not all cytokines are chemokines : chemokines are chemotaxis or chemoattractants.

① stimulate leukocyte movement

② regulate their migration (blood→tissues)

Extracellular pathogens 2

(2)

* chemokines receptors are : seven transmembrane, GTP binding (GPCR)

LAD

* leukocyte Adhesion deficiency : - immunodeficiency disorder.
  - defective B & T cells - leukocytes unable to migrate to site of infection
  - inability to form pus - deficiency in LFA-1/Mac-1
  - deficiency in glycoprotein 150/95 - mutation in CD18 glycoprotein impairs

* Macrophages & dendritic cells present antigens using MHC II & activate T helper cell

* TLR on dendritic cells, activate their expression of ① antigens ② costimulatory molecules ③ cytokines that are all needed for the activation of naive T cells into effector T cell

* Sepsis → sever systemic disseminated infection.

* two rare sequelae of streptococcal infections → produce antibodies to attack the bacterial cell wall protein = M protein.
  - Some of these antibodies may cross react with self antigens.

* Superantigens :- bacterial toxins - resemble conventional antigens
  - can bind to T cell receptor TCR + MHC II
  - non specific activation of T cells
  - stimulate all T cells that express Vβ T cell receptor
  = conventional peptide antigens need binding to (peptide binding cleft although these superantigen can bind without it.