NOTES FOR THIS REVISION DOCUMENT:

- This revision document contains a concise summary of EVERY lecture. They are NOT in the order in which they were given, but rather grouped into a more logical order (e.g. MHC and genetics, primary and secondary immunodeficiencies lectures grouped together). ALL lectures are in here.
- Summaries are divided into 'key facts' (KFs), then Short-Answer Questions (SAQs) and flashcards made by myself.
- Good luck! ☺

LECTURES COVERED:

SAMPLE:

L5 KF: VZV AND VIRAL IMMUNE RESPONSE

- First line of defence = physical/chemical barriers = passive and immediate. Second line = innate immune response, requires activation, 24 hrs, no memory and non-specific. Third line = adaptive, requires activation, 3 days, memory and specific.
- When have viral infection: IFN-a/B respond first, then NK cells, then virus titer peaks and goes down, then virus-specific CTLs, then Ab (remains).

- As an overview of the IR to viral infection: cell use PRRs to detect viral infection and release cytokines (IFN) and chemokines – establish AV state and recruit innate cells. Neutros and NK cells migrate to SOI. DC takes up virus and activates CD8s and CD4s specific to virus (clonal expansion). Effector T cells migrate to SOI. CTLs kill infected cells. Virus-specific Abs are produced by B cells (get help from CD4). Once infection is cleared, many effector cells die, but some memory T and B cells remain.
- TLRs are type 1 integral membrane proteins. Virus specific ones are located within endosomes: TLR3 for dsRNA (HIV), TLR7/8 for ssRNA, TLR9 for CpG DNA. Other TLRs lie on the membrane. Result of TLR activation – NF-kB or IRF transcription factors.
    - NF-kB (through Myd88) leads to pro-inflamm cytokines, chemokine expression, upregulation of endothelial adhesion molecules, upregulation of co-stim (→ adaptive IR). Therefore mostly acute inflammation and stimulation of adaptive IR.
    - IRF route (through TRIF) = expression of type 1 IFNs → induce an antiviral state.
- **<u>Innate IR:</u>**
    - **Cytokines –** regulate innate and adaptive immunity. Mostly pro-inflammatory such as IFNa and B, TNF, IL-1 and IL-6, IFN-y.
    - **Type 1 IFNs =** alpha and beta = mediate early innate IR. These have four functions:
        - Induce AV state in cell and its uninfected neighbours
            - Induces Protein Kinase R (PKR but still requires activation by dsRNA) that phosphorylates EIF2a and inhibits TL – blocks new infectious virion assembly.
            - Induces 2',5'-oligo A synthetase (but still requires activation by dsRNA) – recruits RNAase A – chops up viral RNA.
            - Activation and multmerisation of Mx GTPases – inhibit/prevent gene expression and virion assembly.
        - Increase MHC I expression → link to initiating adaptive.
        - Activate NK cells
        - Stimulate macro and Ab responses → link to adaptive.
    - **NK cells –** lymphocytes that lack Ag-specific surface receptors non-specific). Type 1 ILCs. Respond to IL-12 and IL-15. Found in blood and lymphoid tissue. Kill tumour and virus-infected cells. Function earlier in course of infection than CTLs and recognise targets in different ways. Packed full of cytotoxic granules and express CD16 (FcyRIII).
        - Recognise infected cell via CD16 (look for Abs bound to cell) and induce ADCC, or via MHC I reduction (indicates viral presence).
        - Activated through action of 2 receptor types:
            - An activating receptor – binds heterogenous group of ligands e.g. IgG, HLA, etc. has an ITAM motif. Sends an activating signal to cell.
            - An inhibitory receptor – binds to MHC I if present – has an ITIM motif. Sends an inhibitory signal to cell that dominates activating signal.
            - Therefore when NK cell encounters a normal cell, both receptors will be bound, and NK will not activate. If encounters infected cell, MHC will be downregulated, so only activating receptor will bind and NK will activate = signal to kill.
        - Effector functions: CTL-like mechanism (lyse cell through granzymes/perforin), secrete IFN-y and TNF (stim macro, Ab, more NK, Th1 formation) or ADCC (FcyRIII cross-linking of Ab-opsonized cells and granzymes release). ADCC is active during the intracellular phase of viral infection.
- **<u>Adaptive IR:</u>**
    - CTLs:
        - Recognise virally-infected cells via MHC I Ag presentation and are activated. From a naïve state, require two activating signals from APC = MHC I with antigenic

peptide and co-stim binding to CD28. APCs phagocytose an infected viral cell, therefore perform cross-presentation to express the extracellular antigen on MHC I. Naïve CD8 activates and upregulates chemokine receptors, selectin ligands, integrins, etc.
        - Move to periphery – endothelial cells at SOI upregulate selectins and integrin ligands in response to TNF and IL-1. As the CTLs are mature, can re-activate at SOI without co-stim, just require MHC I (still TCR, CD8, LFA-1 and iCAM-1 interaction).
        - Killing is antigen specific and contact-dependent. Can often have many CTLs contacting one infected cells = many synapses = conjugate formation.
        - MAIN mechanism of killing is via perforin/granzymes. After synapse formation and specific recognition, CTL redistributes cytoskeleton – targeted exocytosis of granules containing perforin and granzymes. Perforin polymerises in the lipid bilayer of the target cell to form a pore – allows entry of granzymes and osmotic lysis. Granzymes are serine proteases – granzymes B cleaves the aspartate residues thus activates pro-caspases and induces apoptosis. CTL detaches so not affected by own action (neighbouring cells are also unharmed due to tight synapse).
        - CTLs can also perform Fas/FasL killing and secrete cytokines, but this was not mentioned in this virology lecture.
    - Abs:
        - Plays different roles depending on where the virus is within the host.
        - Neutralisation = extracellular virus = Ab binds to virus and prevent its binding with a cell surface receptor.
        - ADCC = intracellular virus = Ab binds antigens on the surface of target cells (viral glycoproteins embedded in the membrane) = opsonizes cell and promotes clearance by phagocytes OR via ADCC (NK cells). ADCC occurs if NK cells cross-link (regulatory mechanism) the Fc portion. Cells die via apoptosis.
- Viruses hide/subvert the IR by:
    - Avoiding recognition by Ab e.g. influenzavirus high mutation rate
    - Hiding from the immune system:
        - Hide in neuron e.g. HSV and VZV
        - Establish latent/dormant infection with limit gene expression e.g. herpesivurs
    - Directly infect cells and destroy/alter cells of the immune system e.g. HIV, CMV
    - Encode immunomodulatory gene products that modulate innate/adaptive IR
        - Affect response/activation of the IR
        - Produce “dummy” decoy molecules

L5 SAQ:

1. **Which TLRs are important for viral recognition? Where are they? What do they recognise?**
2. **Compare results of NFkB and IRF activation**
3. **Describe the three mechanisms of the innate IR?**
4. **Describe how type 1 IFNs work (four methods)**
5. **Describe the two mechanisms of the adaptive IR?**
6. **Compare activation of NK cells and CTLs**
7. **Describe VZV infection, its three phases, how it transmits round the body.**