Lecture 4 – Response to Viral Pathogens - Natural Killer (NK) Cells.

Key Points:

- TLR 3, INFα, INFβ
- Antiviral response
- NK cells
- Granzymes, perforin
- MHC level modification by disease

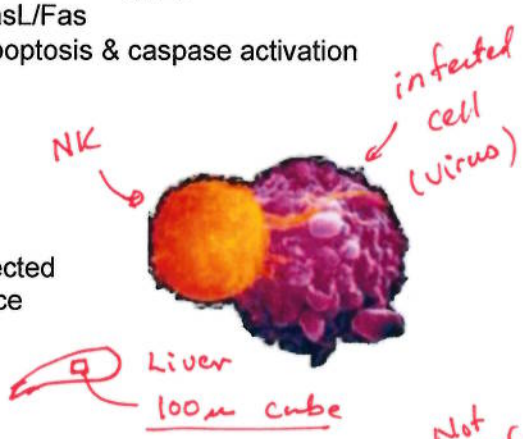
Suggested reading, pg 14

- FasL/Fas
- Apoptosis & caspase activation

Virus infection is detected by several mechanisms:

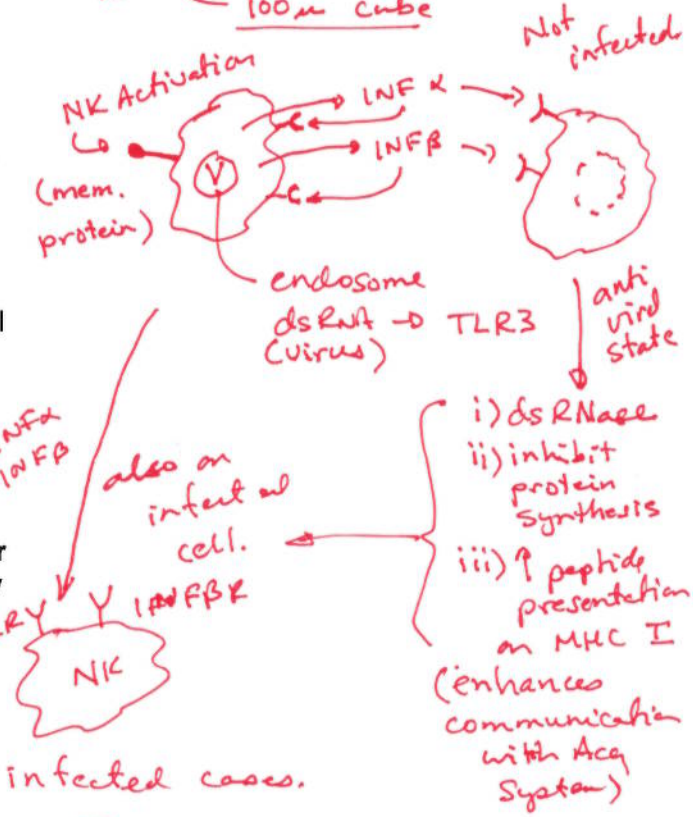
i) Activation of **TLR3** by dsRNA in infected cells.

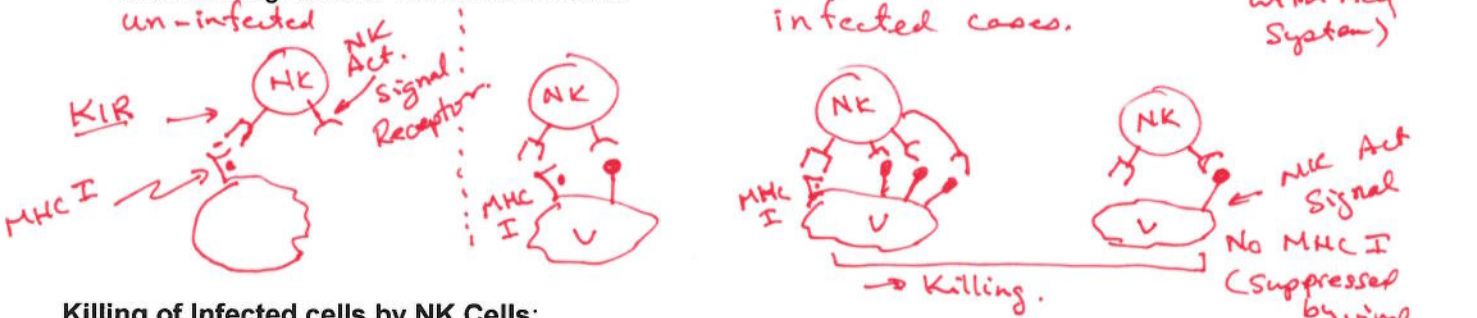
ii) Decrease in MHC I (major histocompatibility) levels on infected cells, leading to their death by NK cells (Many viruses reduce MHC levels to avoid detection by the acquired system.)



Activation of NK Cells vial TLR3

1) TLR 3 signals viral infection, causing production of:
   a. interferon α (**INFα**)
   b. interferon β (**INFβ**),
   c. NK cell *activation* signals.
2) interferons acts in an autocrine and paracrine mode. Inducing anti-viral state in infected and neighboring cells. The anti-viral state is:
   - degradation of dsRNA,
   - inhibition of protein synthesis,
   - enhanced presentation of viral peptides on MHC I – more effective activation of acquired system.
3) NK cells are activated by interferons produced by infected cells and by cytokines from activated macrophages.
4) NK cells are:
   a) Inhibited from killing normal cells by inhibitory signals that are due to MHC binding to **KIR receptor** (killer cell immunoglobulin-like receptor). Killing only occurs if the inhibitory signals are *absent*. A cell with normal MHC will normally not be killed.
   b) Prompted to kill infected and damaged cells by activation signals. Killing requires high levels of activation signals and low levels of MHC.

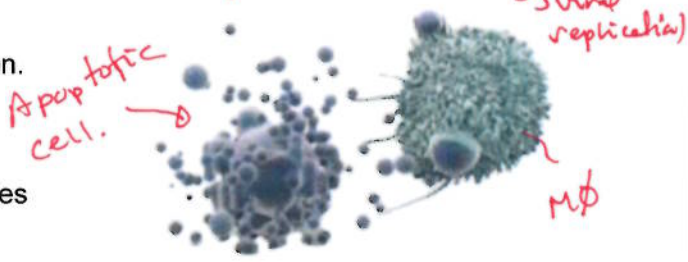




Killing of Infected cells by NK Cells:

A. NK cells typically Induce apoptosis by caspase activation.
Apoptosis – Programmed cell death.

1. Cell shrinkage
2. Chromatin condensation, DNA fragmentation
3. Plasma membrane blebbing, forming apoptoic bodies
4. Apoptoic bodies contain cellular organelles.
5. Apoptoic bodies are cleared by macrophages.



Why is this method of cell death beneficial from an immunological point of view?

i) don't release virus → killed by Mϕ

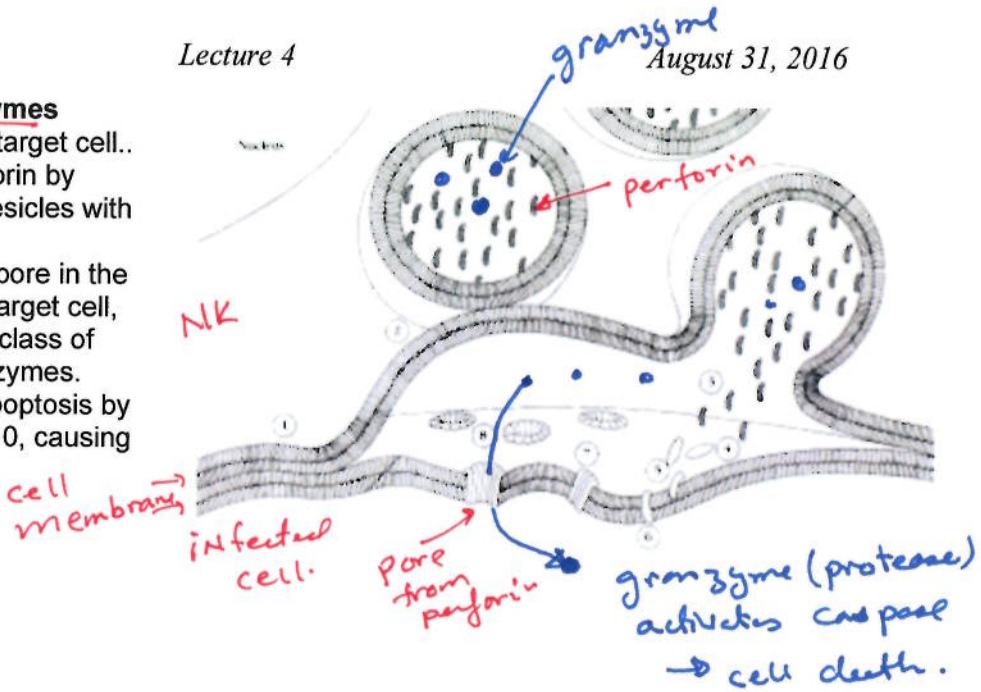
ii) allows macrophage to acquire antigens to communicate to acquired system

A1) Perforin and Granzymes

1. NK cells binds to the target cell..
2. NK cells release perforin by fusion of membrane vesicles with the cell membrane.

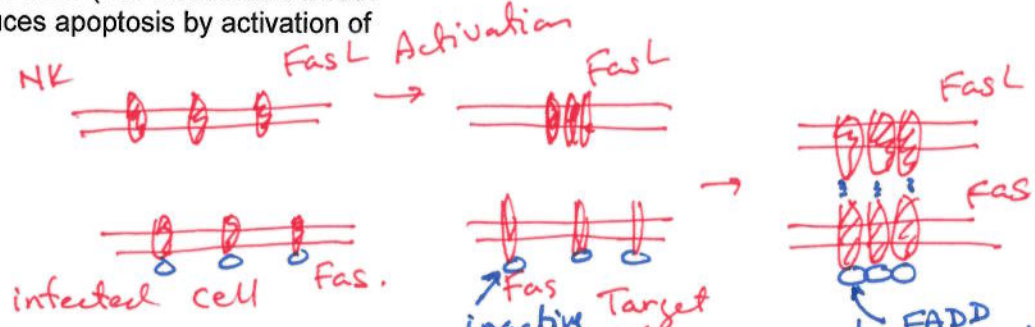
3-8. Perforin generates pore in the cell membrane of the target cell, allowing the entry of a class of proteases called Granzymes.

9. Granzymes induce apoptosis by activation of caspase 10, causing death of target cell.



A2) FasL-Fas

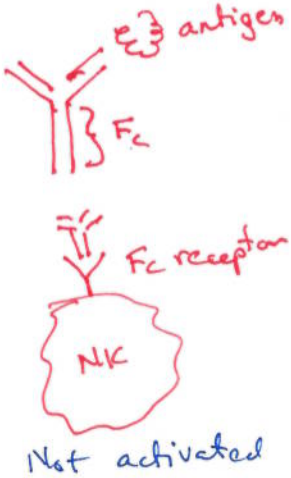
1. Activated NK cells express high levels of FasL, which is a trimer.
3. Binds to Fas on surface of target cells, promoting trimerization of Fas.
4. Trimerization of Fas on target cell activates death domain FADD (Fas Associated Death Domain), induces apoptosis by activation of caspase 8.

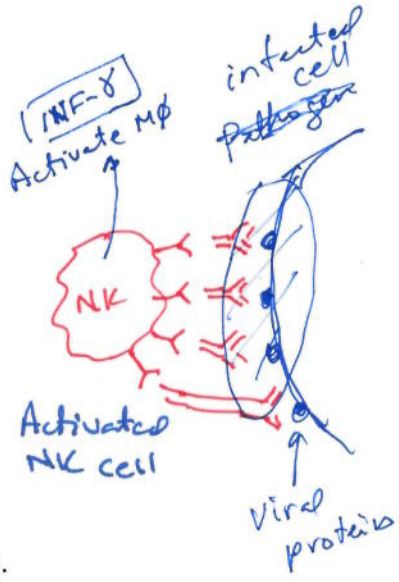


ADCC – Antibody dependent cellular cytotoxicity:

Acq. System

1. NK cell FcR binds to Fc receptors on IgG type antibodies.
2. Low affinity of receptor prevents individual IgG from activating NK cells.
3. Clustering of IgG on pathogen increase chance of binding and activation of Fc receptor – leading to (see above):
   - degranulation releasing perforin and granzymes.
   - release of INF-γ, activating macrophage, and enhancing killing via Fc receptors on macrophages.





Summary of NK Cell-surface receptors:

1. Inhibition receptors (KIR), bind MHC I, inhibit killing.
2. Activation receptors, bind to signals from infected cells, enhance killing.
3. Fc receptors, activation by antibody, resulting in ADCC.