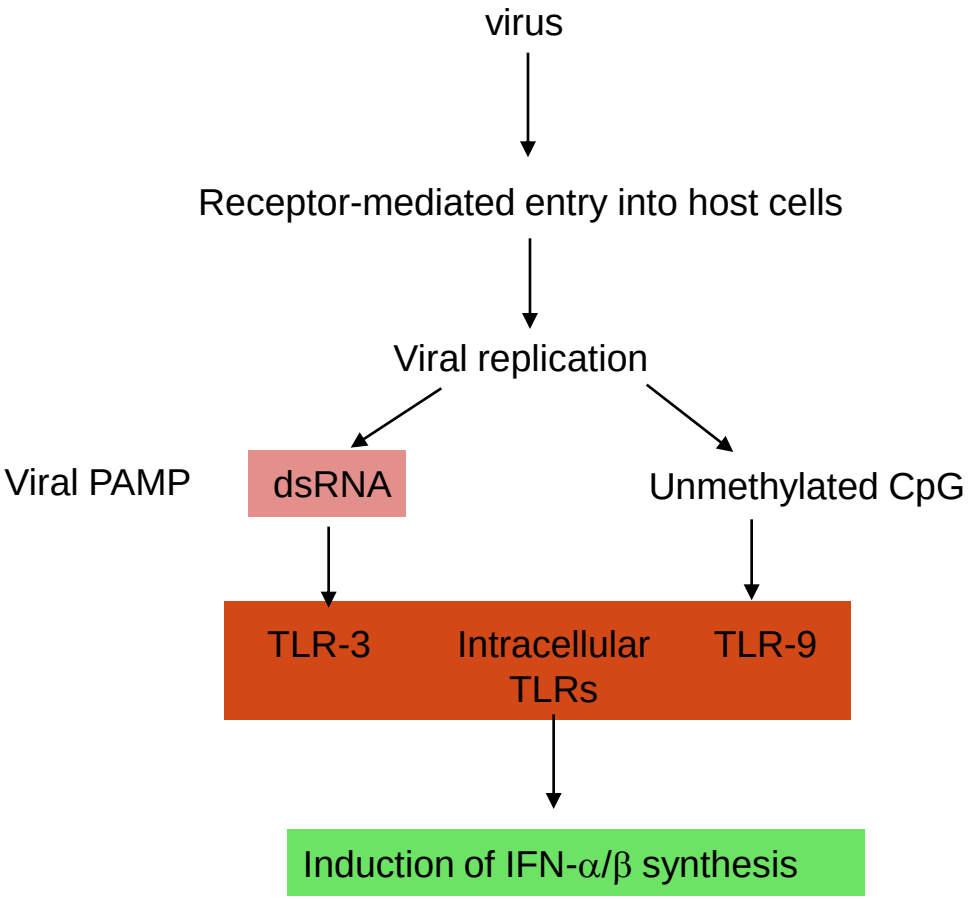
Immune Response to Virus

Fatchiyah

JB UB

Immune Response to Virus

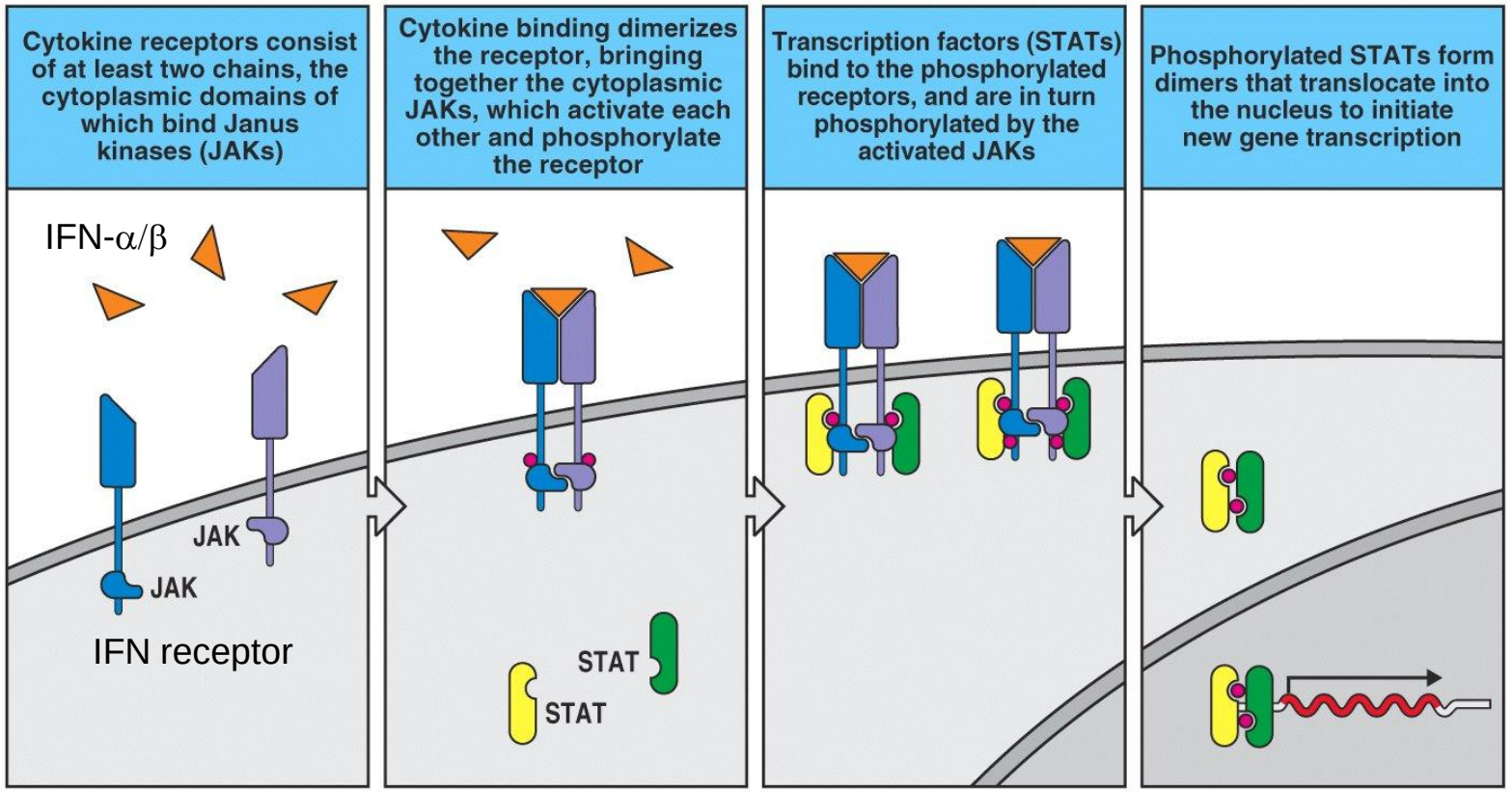
The induction of Interferon (IFN)-α and β



IFN-α/β are type I interferons (many infected cells)
IFN-γ is type II interferon (NK cells, T_H1, CTL)

Interferon α/β activate many anti-viral genes.

IFN α/β binds to IFN receptor to activate STAT (signal transducers and activators of transcription). STAT activates the transcription of many anti-viral genes.



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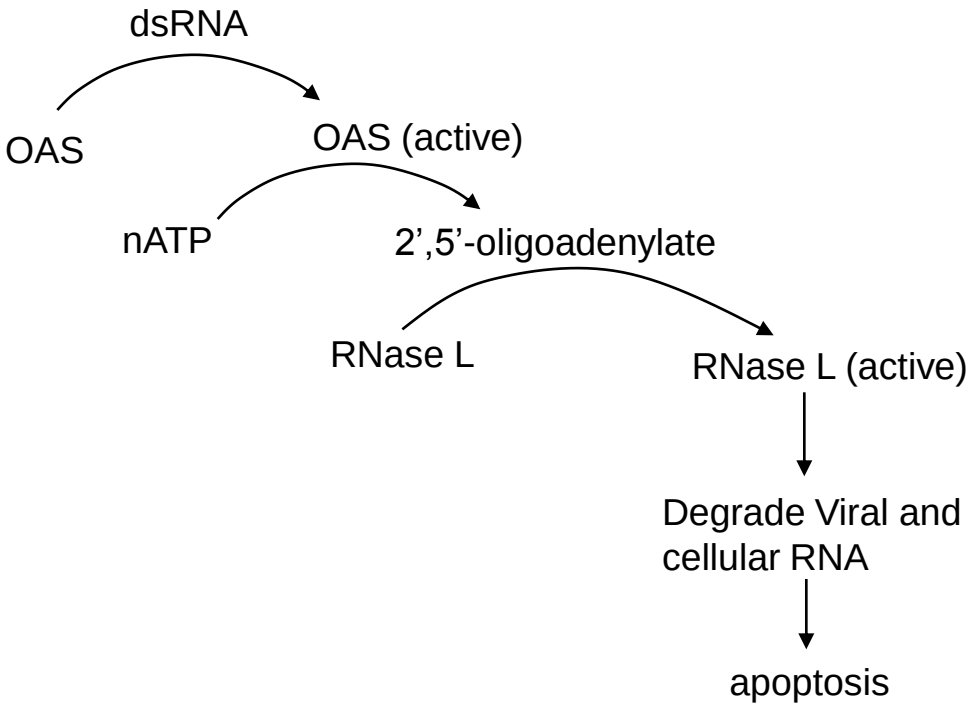
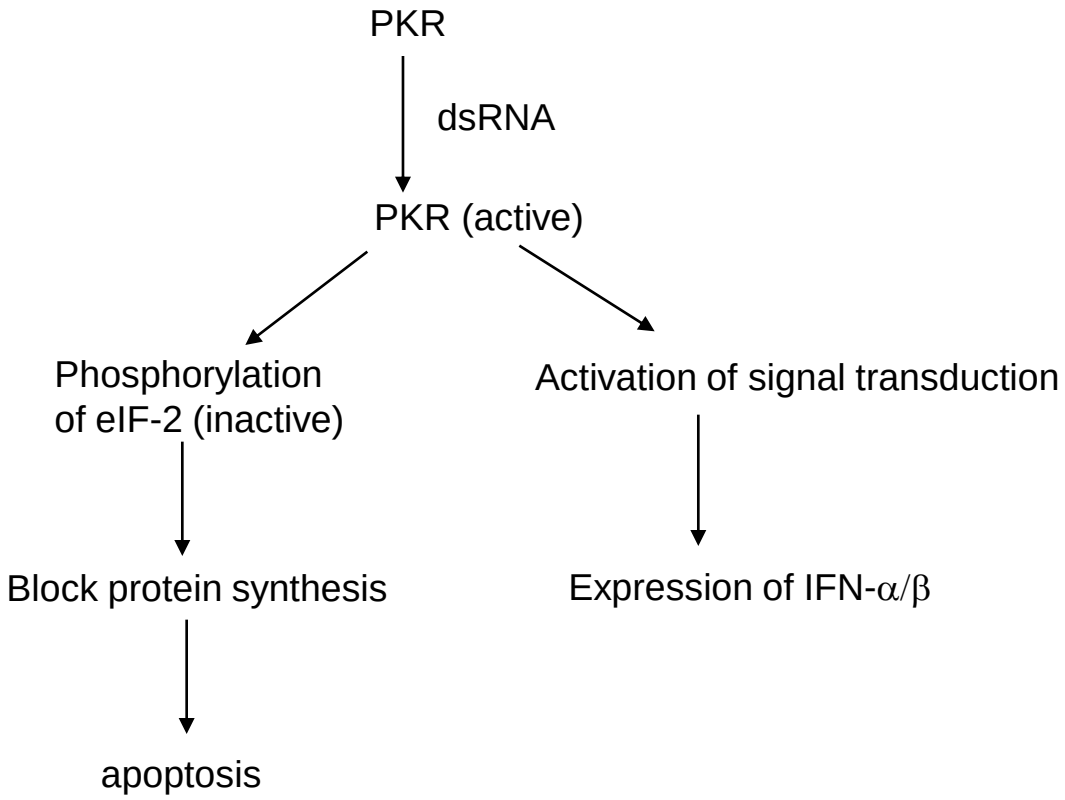
IFN-α/β induces the expression of 2'-5'-oligoadenylate synthetase (OAS).



Some OAS can induce apoptosis more directly by sequestration of anti-apoptotic proteins such as Bcl2.

IFN-α/β induces the expression of PKR kinase.

PKR kinase: serine threonine kinase.
Constitutively expressed but upregulated by IFN-α/β.
Contains dsRNA binding domains, and serves as intracellular sensor of viral infection.



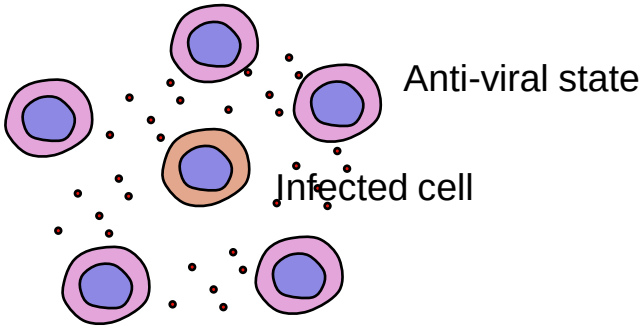
- IFN-α/β induces the expression of Mx proteins.

  Mx-A and Mx-B can block transcription of virus genome by inhibiting viral polymerase complex.

  A related protein GBP (guanylate-binding protein) may block the assembly of viral particle.

- IFN-α/β upregulates the expression of class I MHC for antigen presentation.

- IFN-α/β activates NK cells.



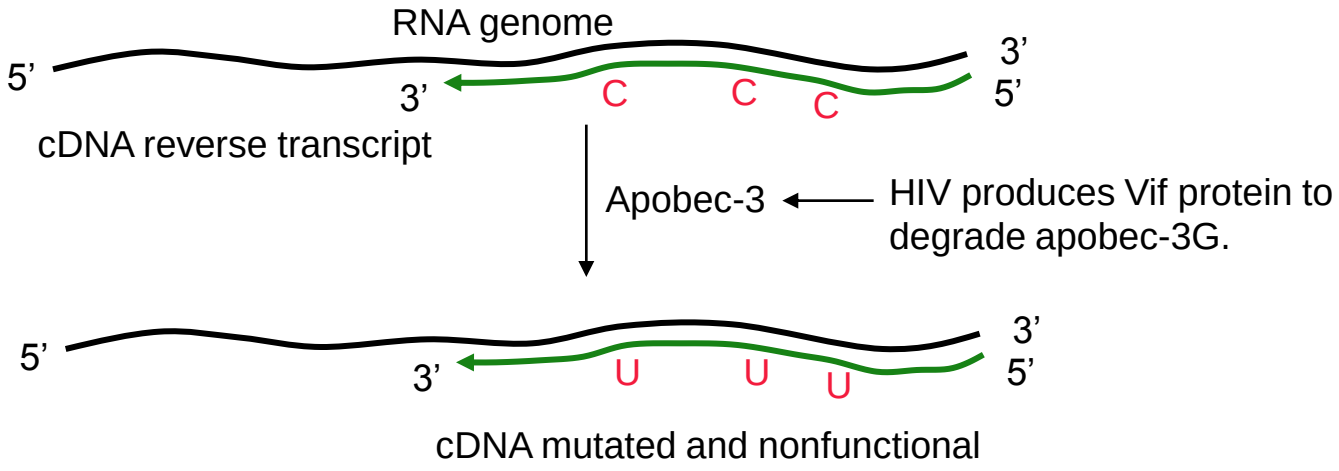
INF-α/β leads to anti-viral state in neighboring cells.

Inactivating retrovirus by cytidine deamination

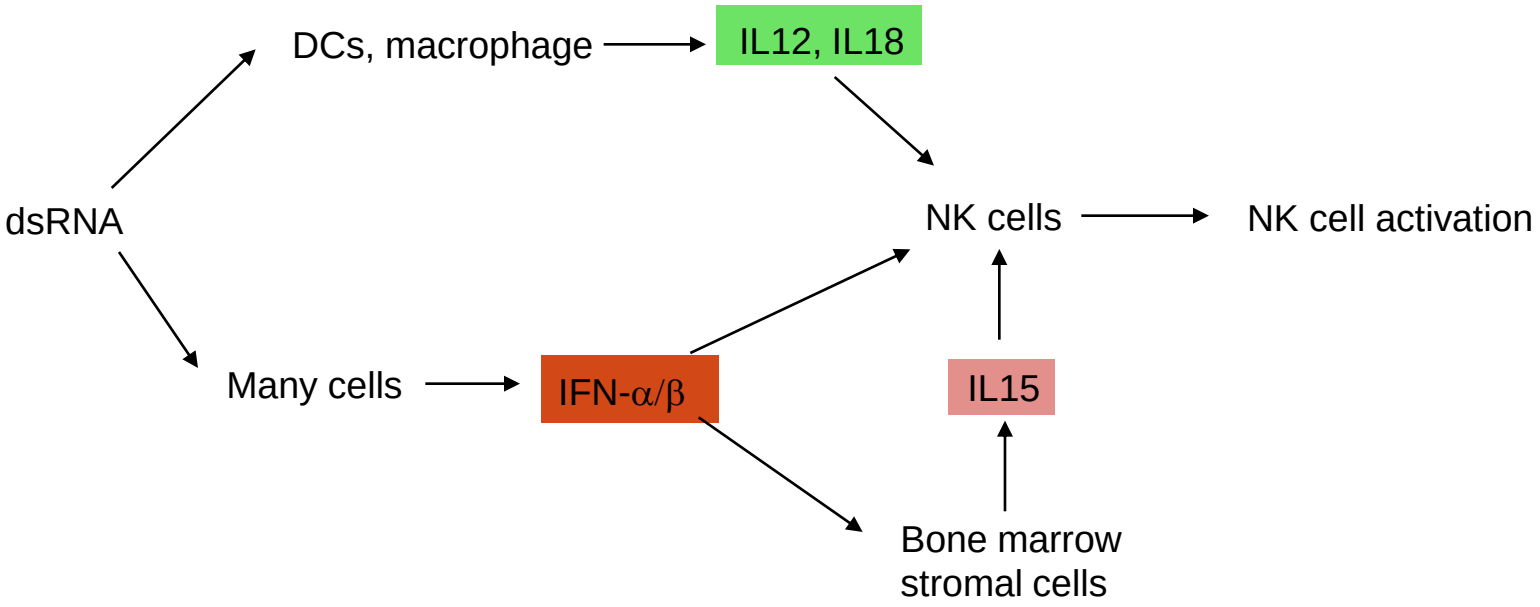
Apobec-3 (A-H): homologous to AID.
The seven apobec-3 genes are located in one cluster.

AID deaminates cytidines in switch region (class switching) and V region (somatic hypermutation).

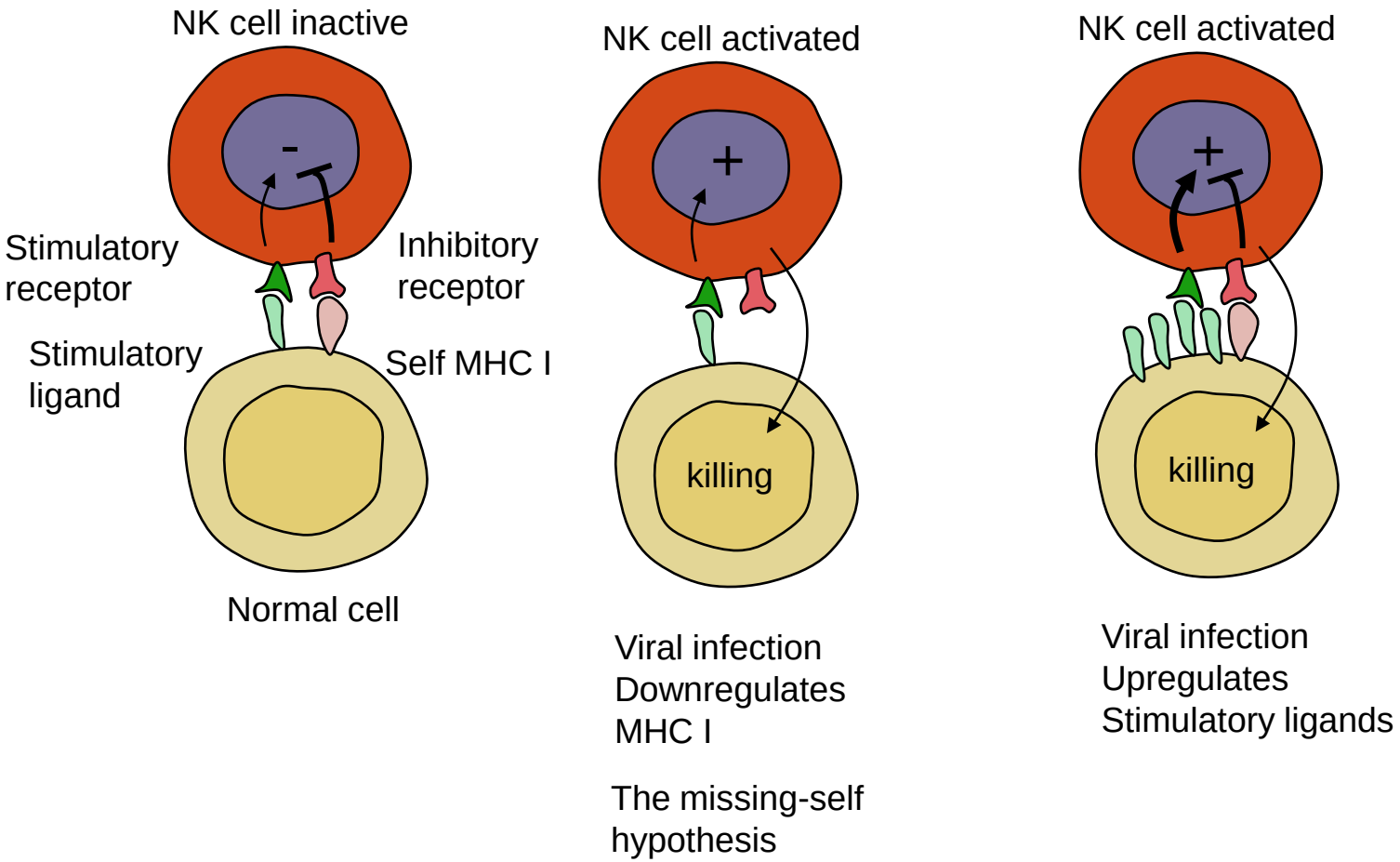
Apobec-3B, F, G deaminates cytidines in reverse transcript during retroviral replication.



Cytokines activates NK cells.



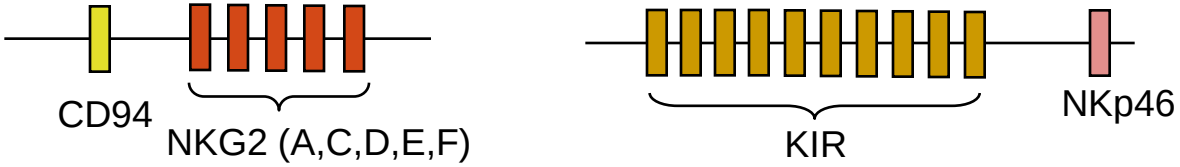
NK cell activity is regulated by stimulatory and Inhibitory receptors.



NK receptors

Human NK cell
- CD94/NKG2 (lectin type of receptors)
- KIR (killer cell immunoglobulin-like receptors, Ig superfamily)
- NKp46, NKp30, NKp44 (Ig superfamily)

The NK receptors are encoded in gene clusters.

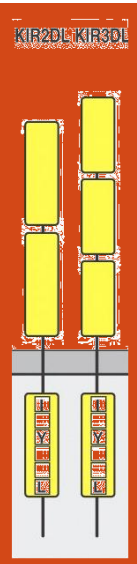


Mouse NK cell
- CD94/NKG2 (lectin type of receptors)
- Ly49 (lectin type of receptors)

Inhibitory receptors

Inhibitory receptors contain ITIM (immunoreceptor tyrosine-based inhibitory motif) in their cytoplasmic domains.

[I/V]XYXXL: Y is the substrate of tyrosine kinases.
Phosphorylated ITIM recruits phosphatases (SHP-1) that counteract the Phosphorylation cascade of signal transduction.

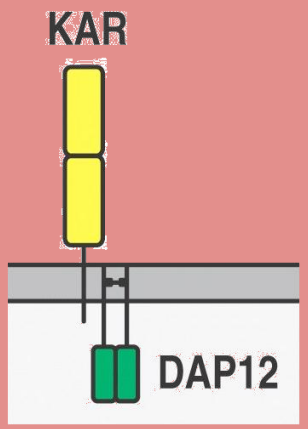


ITIM

Stimulatory receptors

Stimulatory receptors contain short cytoplasmic domain without ITIM.
The transmembrane domain associates with signal transduction molecules that contain ITAM (immunoreceptor
Tyrosine-based activating motif) in the cytoplasmic domain.

YXX[L/I]X6-9YXX[L/I]: Y is the substrate of typrosine kinases.
Phosphorylated ITAM recruits and activates additional kinases for signal transduction.



ITAM

ITAM and ITIM are common motifs in many immune receptors

ITAM

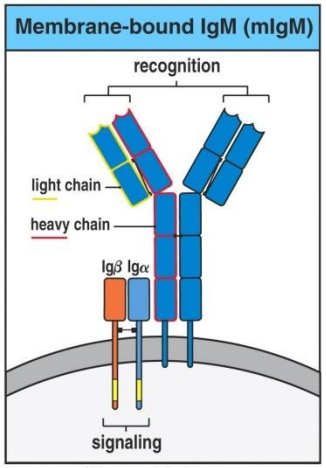


Figure 6-8 Immunobiology, 6/e. (© Garland Science 2005)

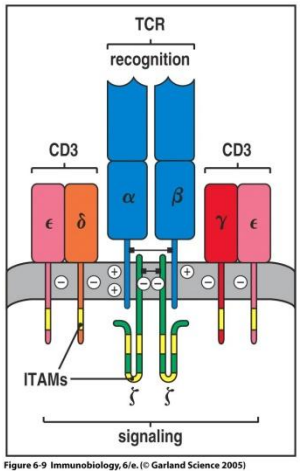


Figure 6-9 Immunobiology, 6/e. (© Garland Science 2005)

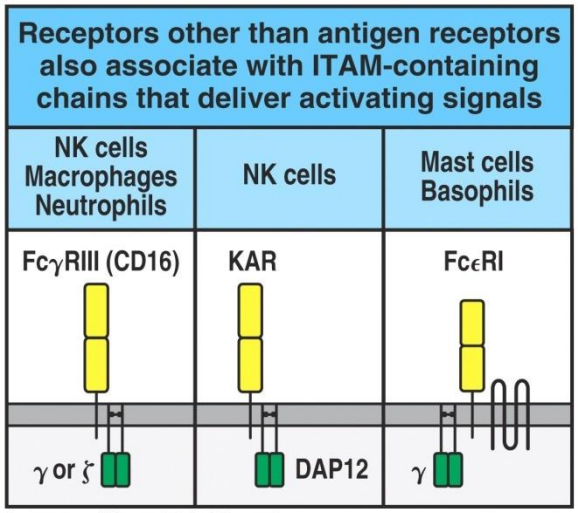


Figure 6-19 Immunobiology, 6/e. (© Garland Science 2005)

ITIM

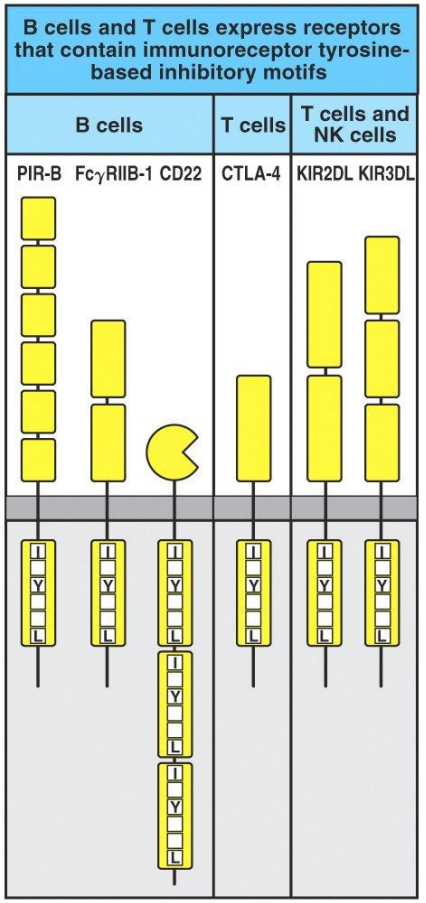
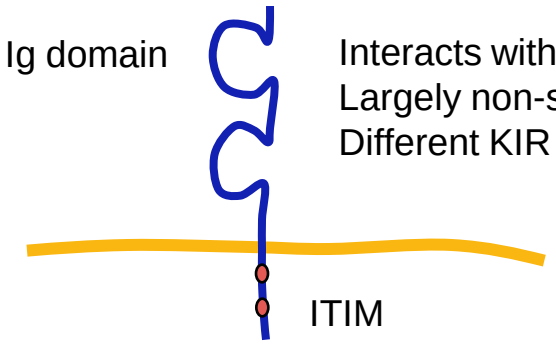


Figure 6-20 Immunobiology, 6/e. (© Garland Science 2005)

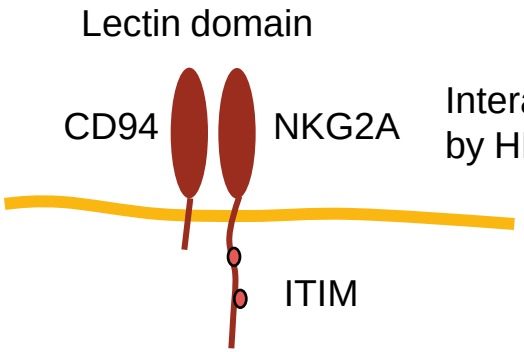
Inhibitory receptors interact with Class Ia MHC (classical class I MHC).

(KIR) Killer immunoglobulin like receptors



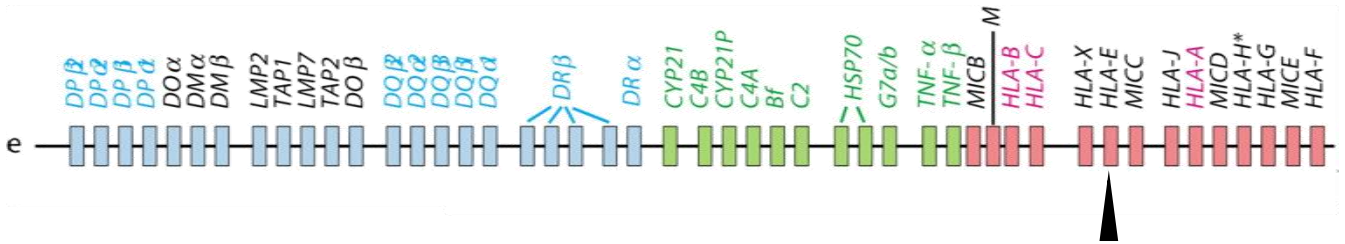
Interacts with MHC (HLA-A, B, C)
Largely non-specific for peptide sequence
Different KIR interacts with different HLA alleles

CD94/NKG2A (lectin like receptor)



Interacts with a specific peptide presented by HLA-E (class Ib MHC, nonclassical MHC).

CD94/NKG2A recognizes Class Ia MHC indirectly.



The ligand is composed on HLA-E (class Ib, non-classical MHC) and a nine-amino acid peptide derived from the cleaved signal sequence of HLA-A, B, C.

Signal peptide

MGAMAPRTLLLLLAAALGPTQTRA-classIa-MHC

Peptide/HLA-E recognized by CD94/NKG2A

In the absence of the peptide, HLA-E is unstable and fails to be expressed on cell surface.

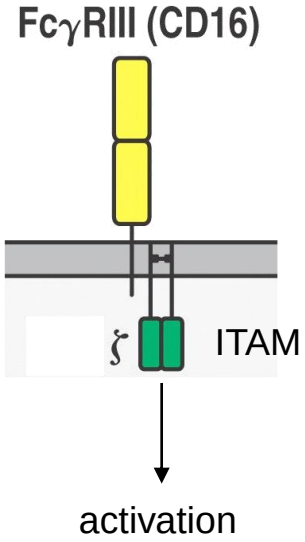
The loading of the signal peptide onto HLA-E is dependent on TAP.
CD94/NKG2-HLA-E interaction monitor the expression of Class Ia MHC as well as the function of the antigen presentation system.

Stimulatory receptors for non-MHC ligands

CD16 (FcγRIII)

A high affinity receptor for IgG (IgG1,IgG3, human, IgG2a in mouse).
CD16 associates with a signaling molecule containing ITAM.
Binding of IgG-coated antigen activates NK cell.

Antibody-dependent cellular cytotoxicity (ADCC)



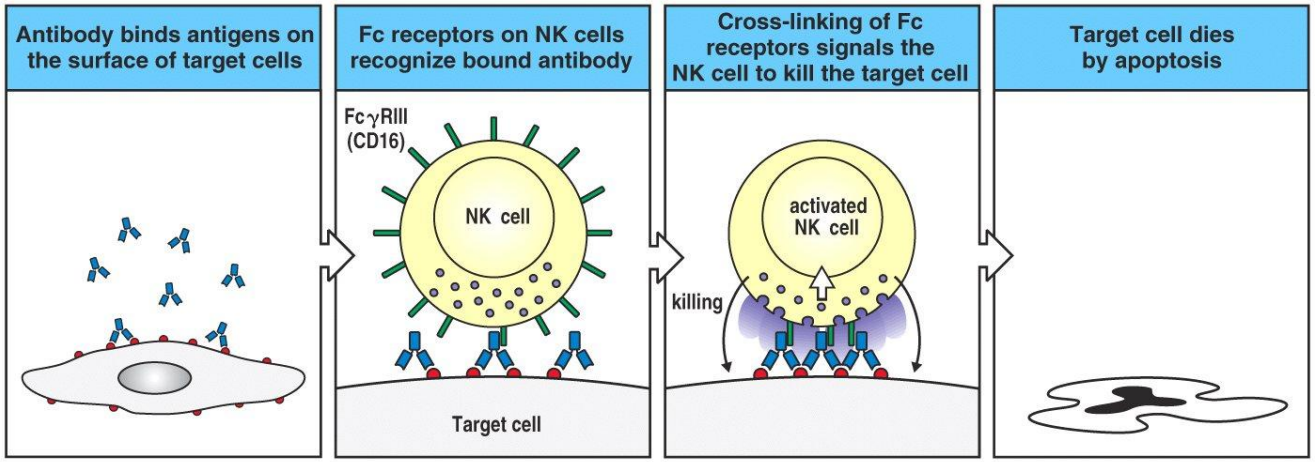
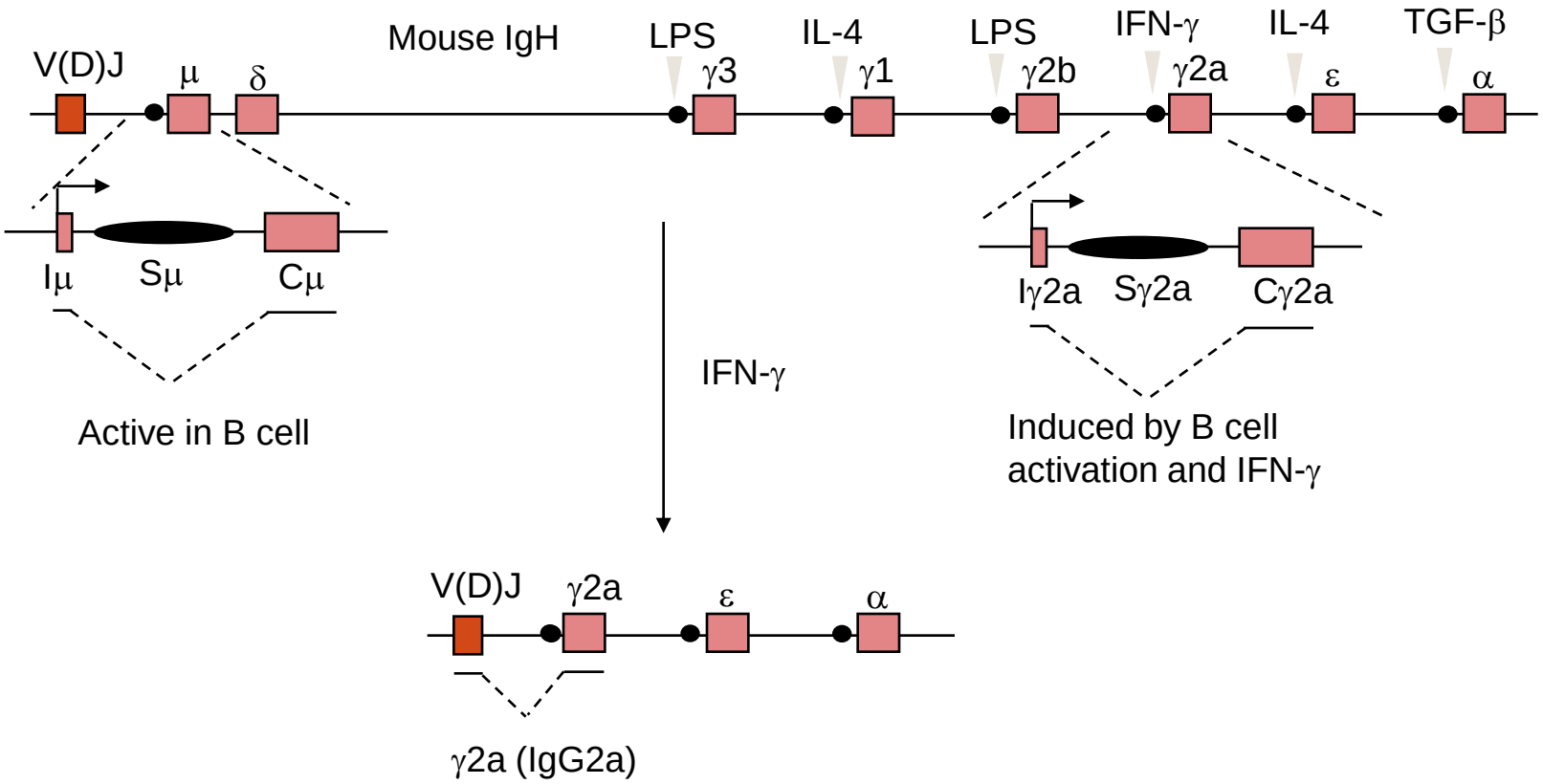


Figure 9-34 Immunobiology, 6/e. (© Garland Science 2005)

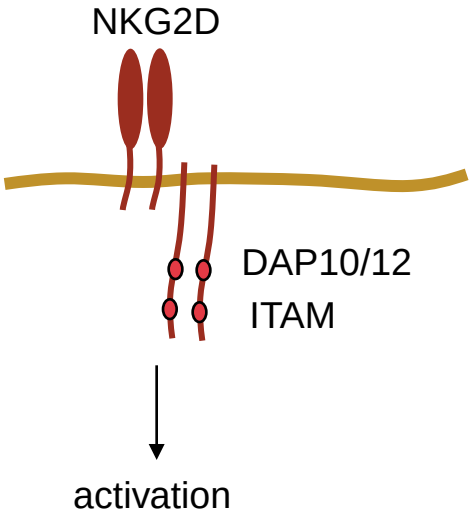
Class switching to IgG2a is induced by IFN-γ during immune response to viral infection.

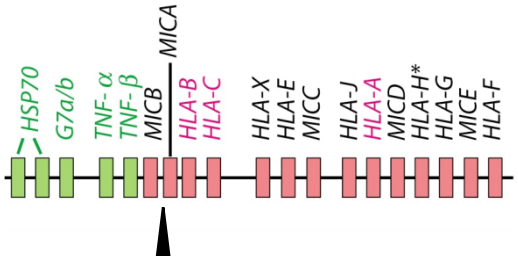


IgG2a facilitates ADCC by NK cells during viral infection.

NKG2D is a stimulatory receptor.

NKG2D differs from NKG2A,C,E,F, and does not associate with CD94.





Ligands are MICA and MICB

MICA and MICB are distantly related to Class I MHC in sequence and overall structure.

The location of peptide binding groove is closed. They do not bind peptide.

MICA is expressed by some intestinal epithelial cells, but not by other cells.
Upon transformation, infection, MICA, MICB are strongly induced.

No MICA, MICB in mice. Mice have Rae1, H60. Humans have ULBPs or RAET1.
Have similar structure to MHC I.

NKp46, NKp30, NKp44 are stimulatory receptors.

All three are Ig SF members.
NKp46-CD3ζ, NKp30-CD3ζ, NKp44-KARAP/DAP12

The ligands are not known.

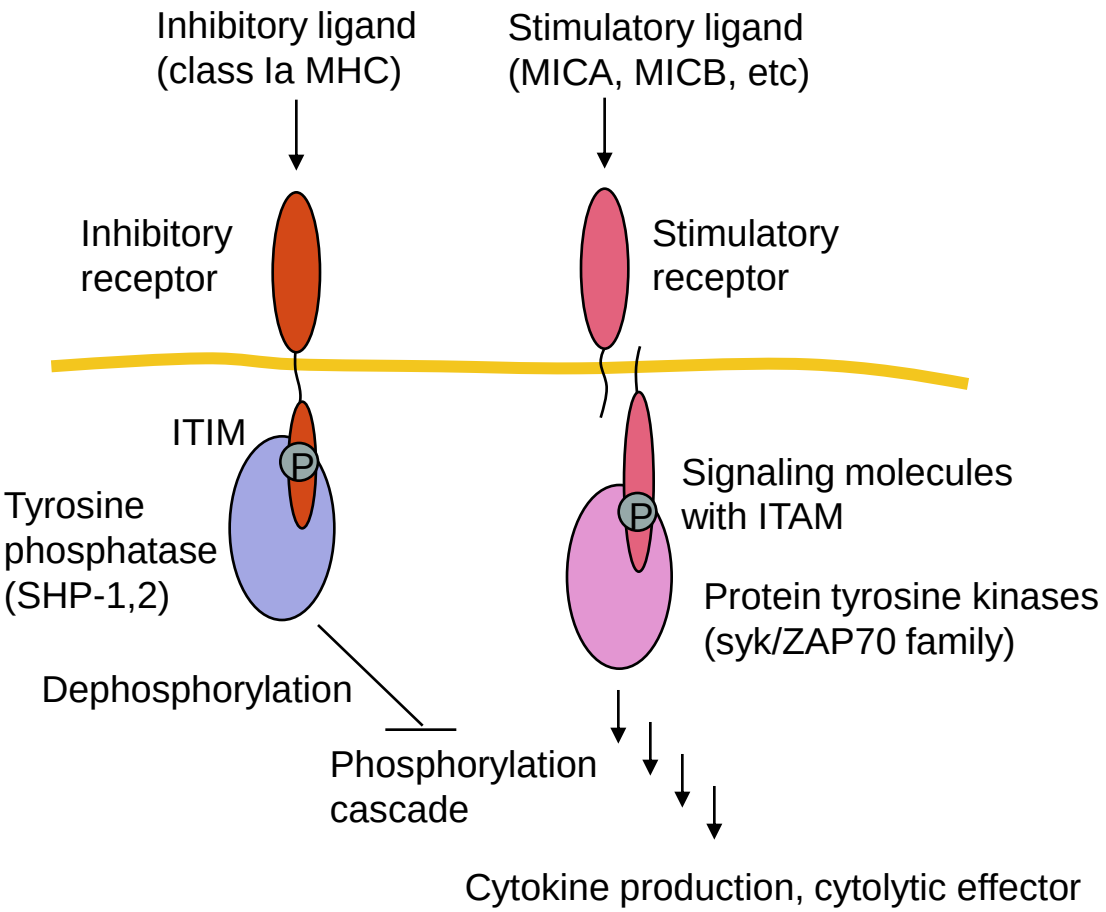
Some stimulatory receptors recognize Class Ia MHC.

The simulatory receptors may in fact bind viral MHC decoys.
Mouse Ly49H (stimulatory receptor) confers resistance to MCMV.
It binds viral product m157, which is structurally related to class I MHC.

The stimulatory receptors may bind MHC complexed with particular pathogen peptides.

Stimulatory receptors generally bind MHC with lower affinities than the inhibitory receptors.
Viral infection leads to the production of interferons, which upregulate MHC expression.
This could saturate the interaction with both stimulatory and inhibitory receptors and lead to the activation of NK cells.

NK cell activation status depends on the Integration of both stimulatory and inhibitory signals



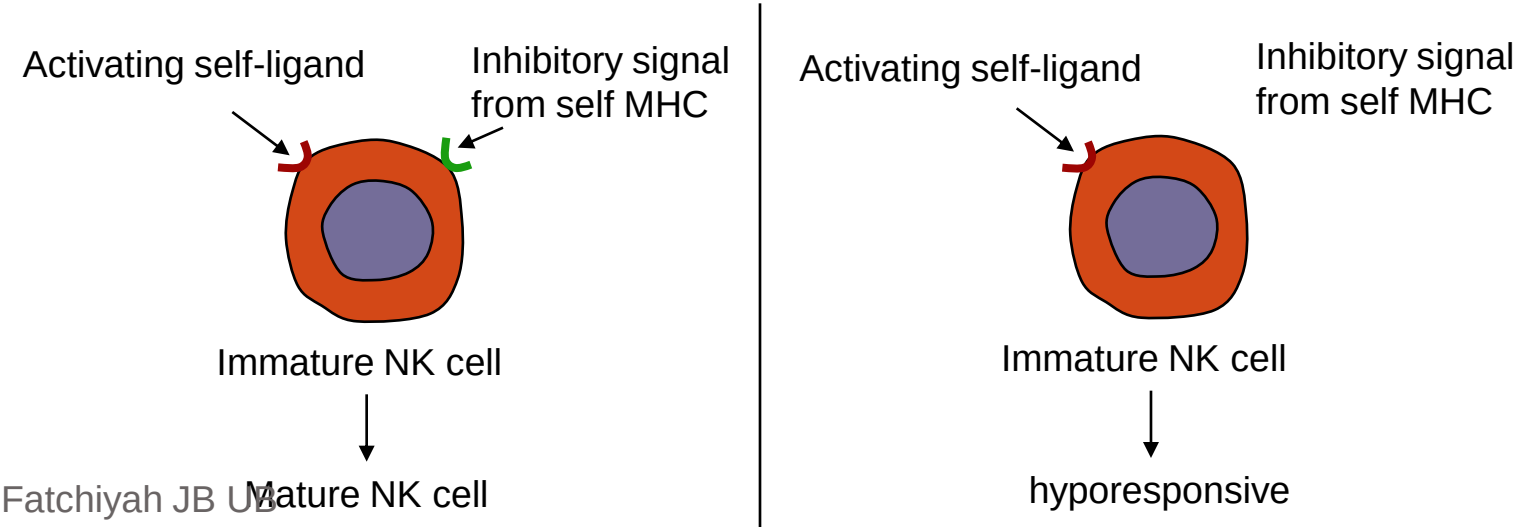
Each NK cell expresses a subset of receptors (on average 4/cell).

The expression of each receptor is largely random.

In general, each NK cell expresses at least one inhibitory receptor for self-class Ia MHC
To prevent the attack of normal host cell.

Self tolerance of NK cells

There are NK cells that do not express inhibitory receptor for self-MHC.
These cells tend to be hyporesponsive (anergy).
During NK cell maturation, interaction with activating ligands without inhibitory signal leads to a hyporesponsive state.



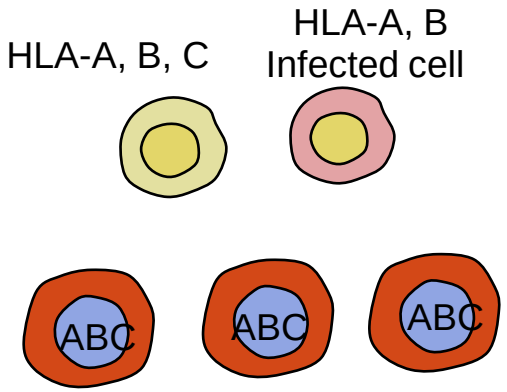
NK receptor expression patthern is established during maturation

The various Ly49 receptors in mice are expressed largely randomly.

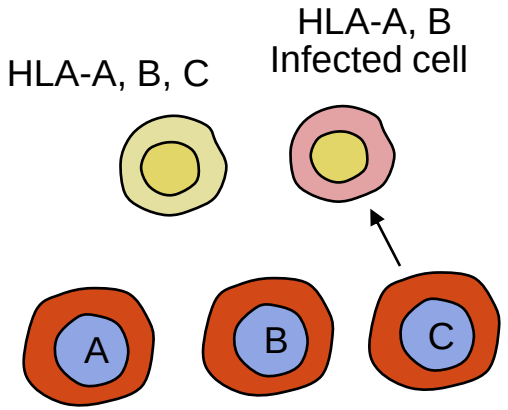
Expression of a Ly49 receptor that strongly interact with self-class Ia MHC inhibits the expression of new receptors (Analogous to allelic exclusion in B and T cells).

If a NK cell does not express a Ly49 receptor specific for self-MHC, such cell exhibit a hyporesponse phenotype.

This pattern prevents the production of NK cells that are over-inhibited and cannot respond to modest reduction of MHC in infected or transformed cells.



If each NK cell expresses all the inhibitory receptors, loss of one MHC I will not lead to NK attack.



If each NK cell expresses a subset of inhibitory receptor, loss of one MHC will activate a subpopulation of NK cells.

NK cell effector functions

Secretion of IFN-γ and TNF-α.

IFN-γ is produced by CTL and T_H1 cells as well.
At the early stage of viral infection, IFN-γ is produced primarily by NK cells.

IFN-γ can active macrophage, which contribute to immune response to intra-cellular bacteria and virus.

IFN-γ stimulates antigen presentation by class I MHC, PA28, TAP.
IFN-γ induces the expression level of MHC I and MHC II.
IFN-γ facilitates the differentiation of CD4 T cells into T_H1 lineage.
IFN-γ promotes the class switching to IgG2a, which mediates ADCC by NK cells.

} Activate The adaptive Immune Response To virus

cytotoxicity

- cytotoxic granules.
  - perforin → Lysis of target cell
  - Granzyme B → Apoptosis of target cell
- Fas-FasL pathways. → Apoptosis of taget cell

NK cells control viral infection in the first few days of immune response.
Complete elimination of the infection requires adaptive immunity.

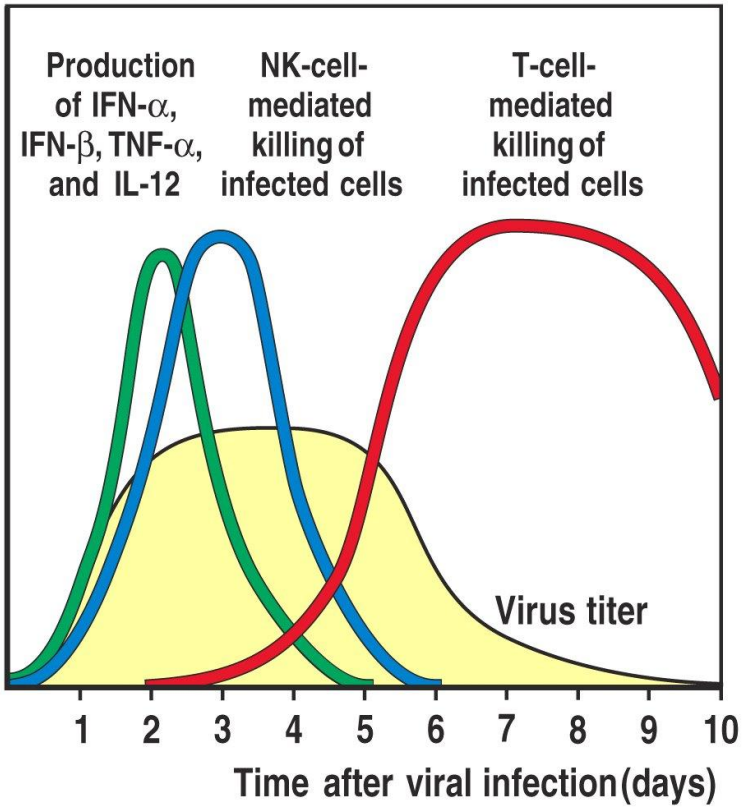
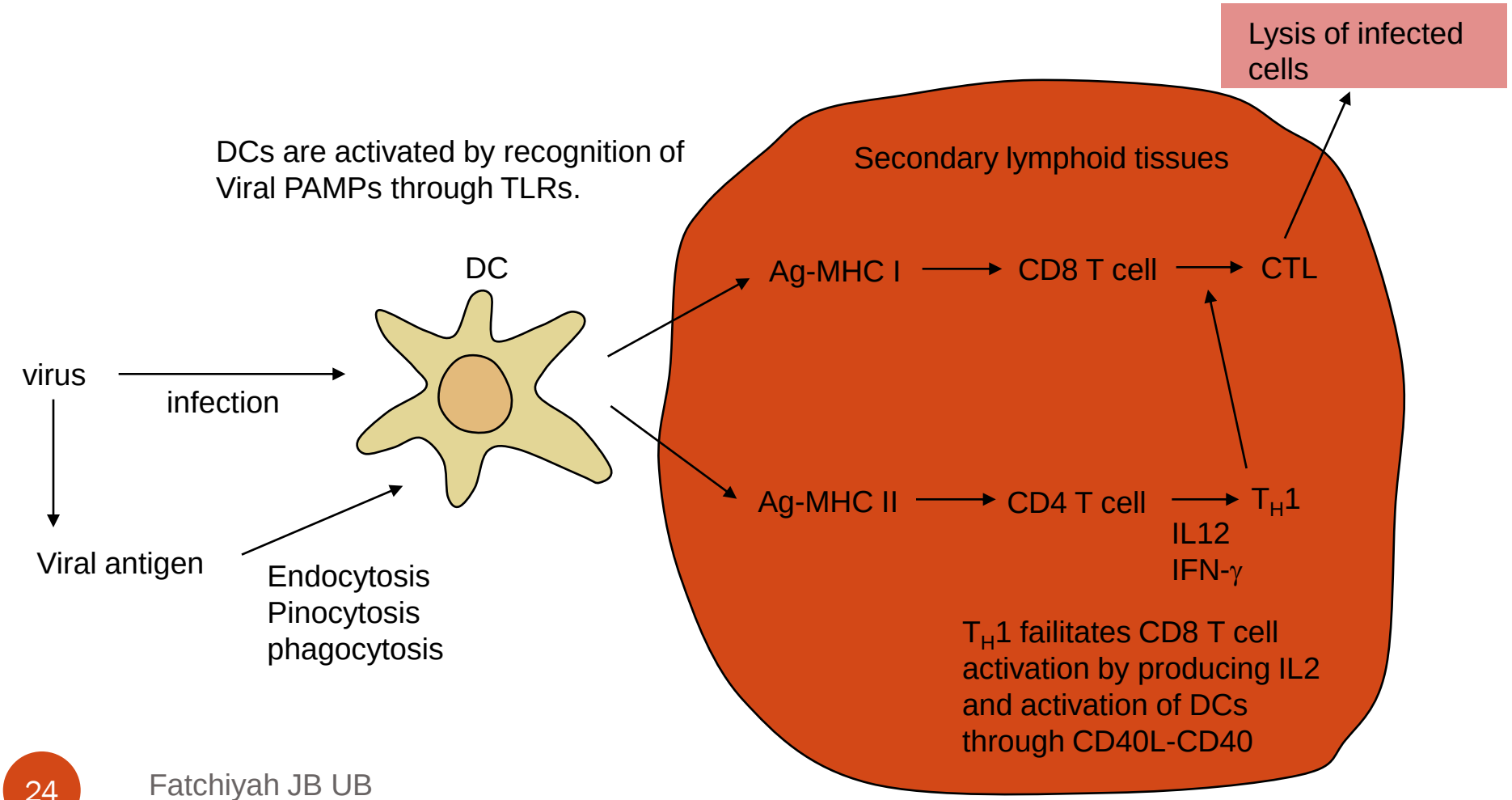


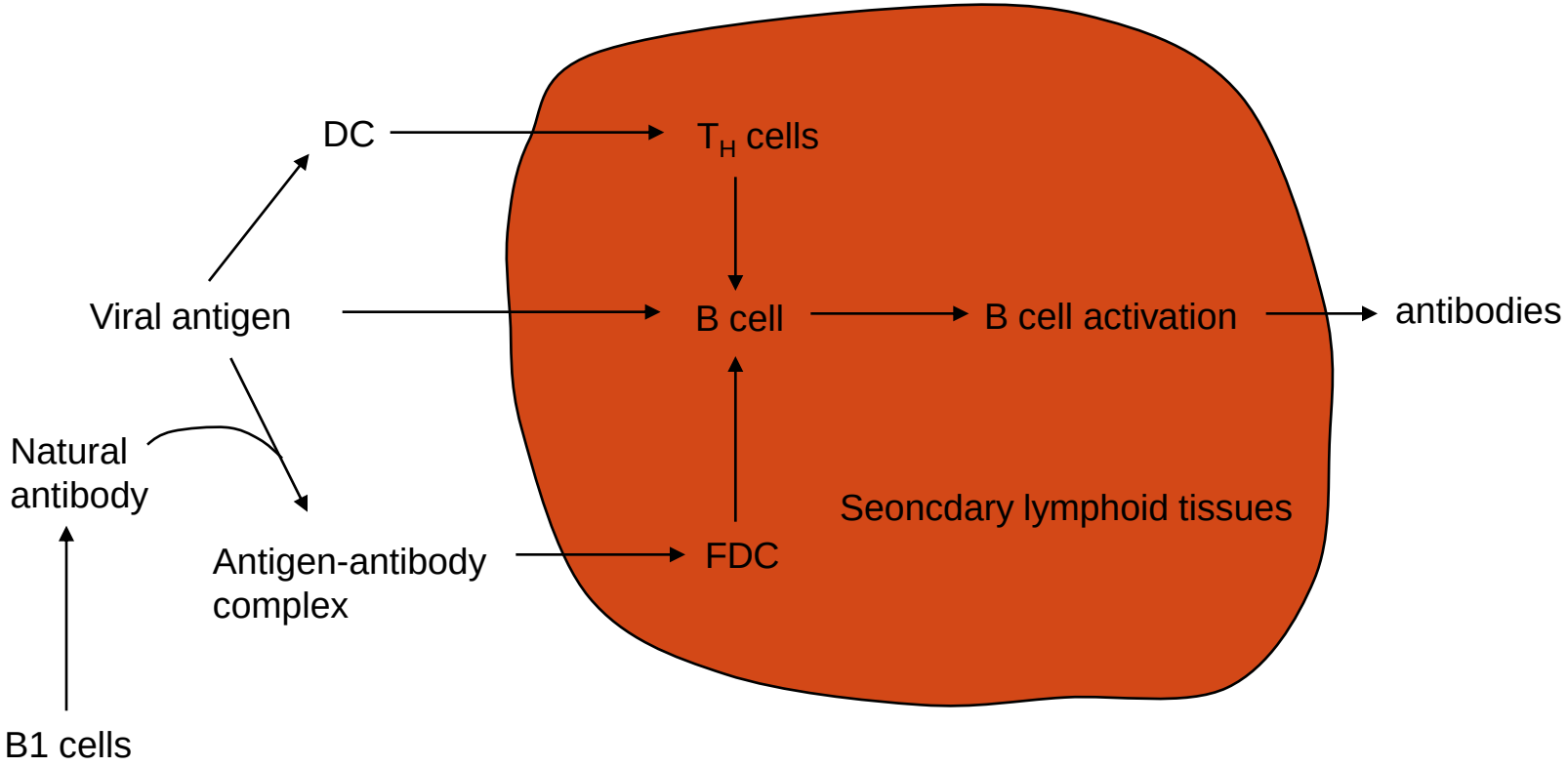
Figure 2-49 Immunobiology, 6/e. (© Garland Science 2005)

T cell activation

DCs can be directly infected by virus.
If DCs are not infected by virus, DCs can still internalize viral antigens from the suroundings through phagocytosis, endocytosis and macropinocytosis.
The antigens can be presented in the context of both class II and class I MHC through cross-priming.



B cell activation

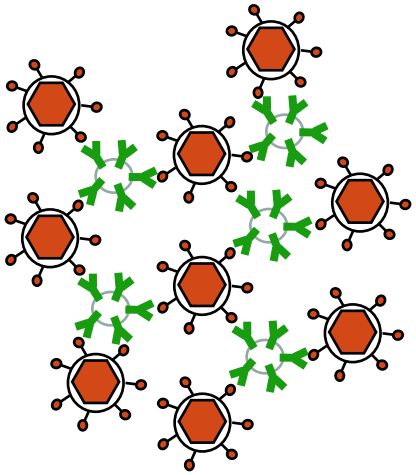


The effector functions of antibodies

Antibodies to viruses can inhibit the infection of viruses to other cells and prevent the spread of infection.

Antibodies can activate complement to lyse enveloped viruses.

Opsonization can facilitate phagocytosis.



Crosslinking of antigens to form a aggregate

IgM most effective

(agglutination)

Complement activation

C3b and antibodies serve as opsonins for Phagocytosis.

Immunological memory

Antigen-antibody complex can be retained on FDC for long periods of time and cause periodic activation of B cells.

Memory T and B cells.

The death of activated T effector cells.

Involves FAS and FasL. Defects in Fas and FasL cause lymphoproliferative and autoimune phenotype (lpr and gld) in mice.

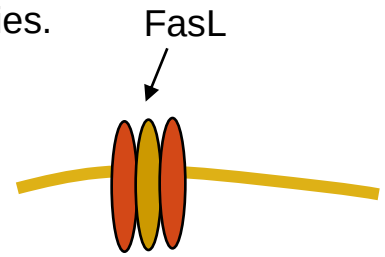
In humans, this defect causes ALPS (autoimmune lymphoproliferative syndrome).

The patients are characterized with enlarged spleen and lymph nodes with no overt signs of infection.

Have elevated levels of immunoglobulin in serum and develop autoantibodies.

Predisposed to develop lymphomas.

The genetic defect is in Fas gene. The mutation is dominant negative.
Activaeted T and B cells do not undergo Fas-mediated apoptosis.

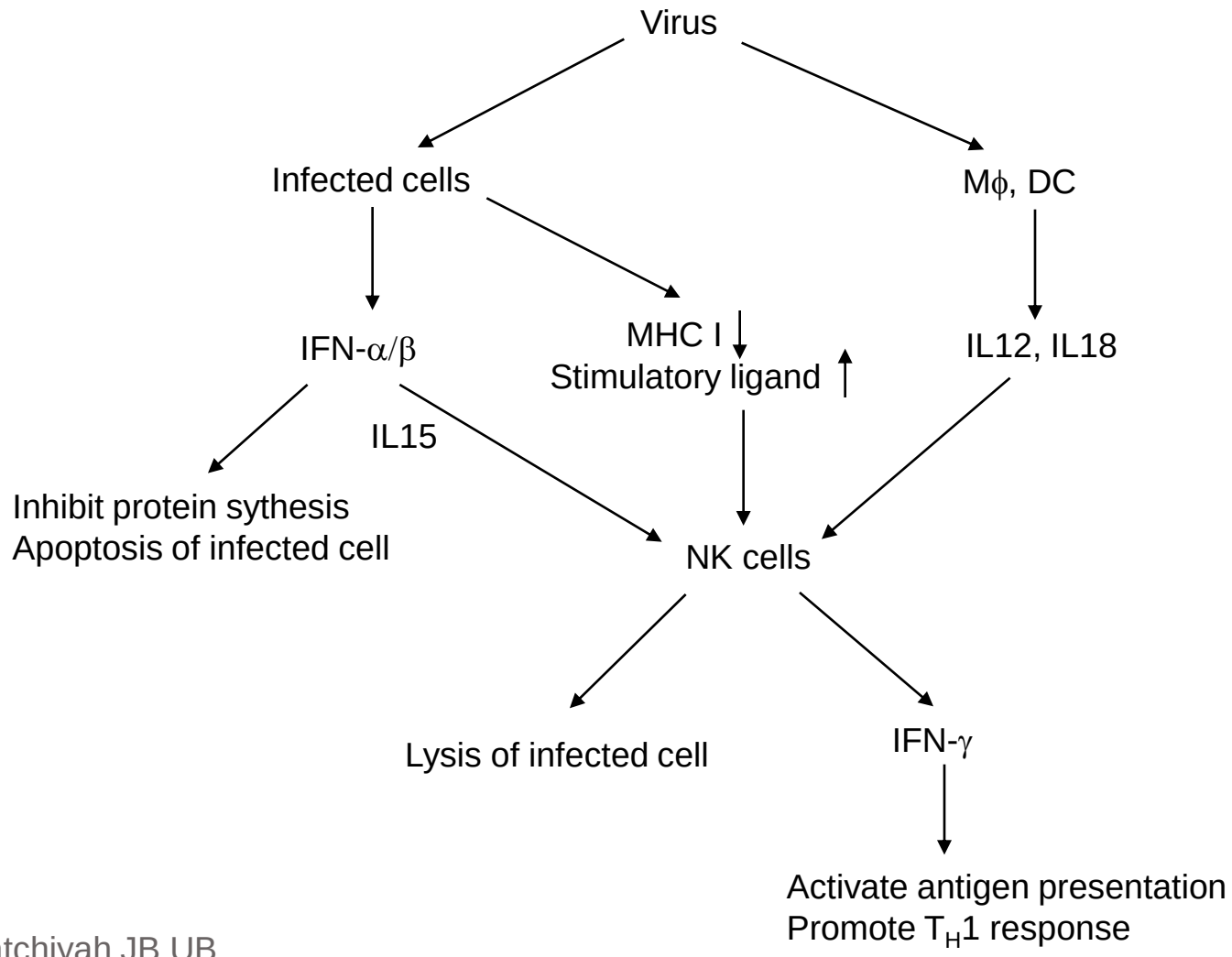


Fas is a trimer

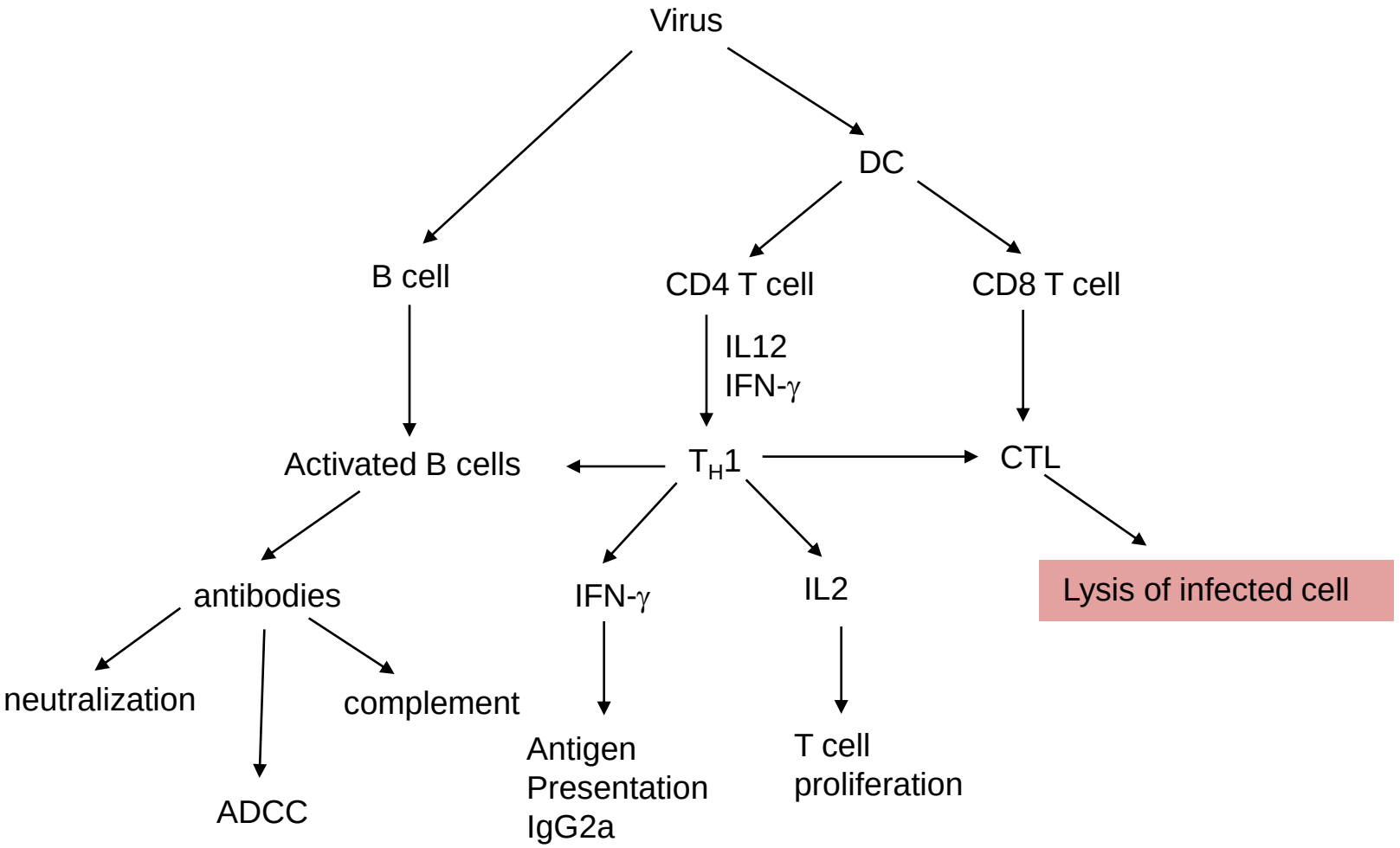
One mutant copy renders the receptor inactive

Immune Response to Virus

Innate immunity



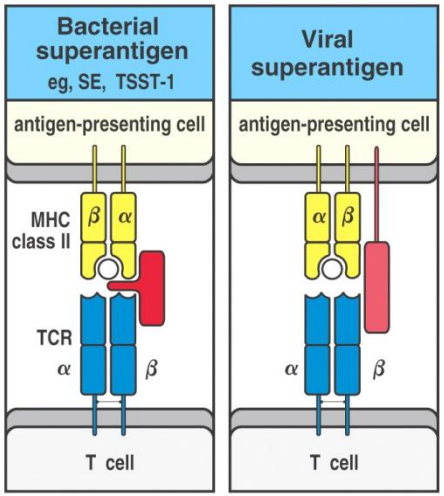
Adaptive Immunity

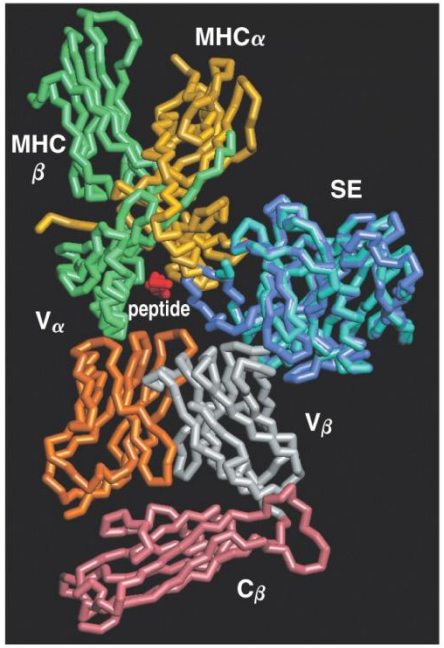


Superantigen

Viral superantigen: mouse mammary tumor virus, rabies virus, Epstein-Barr virus

Bacteria superantigen: staphylococcal enterotoxins (SEs, foodpoisoning)
toxic shock syndrome toxin-1 (TSST-1, toxic shock syndrome)





Superantigens crosslink class II MHC with TCR Vβ chain.

The interaction is independent of Peptide sequence.

Each superantigen can bind 2-20% of all T cells.

Superantigens are not processed and presented by MHC.

Superantigens can cause massive activation of CD4 T cells, which release cytokines (IFN-γ, TNF-α) and activate macrophages to release inflammatory cytokines (IL1, TNF-α) These cytokines cause the toxic shock syndrome (similar to septic shock).

The massive activation of CD4 T cells eventually lead to their death, and cause immunol suppression, which aid the propagation of pathogens.

Latent viral infection

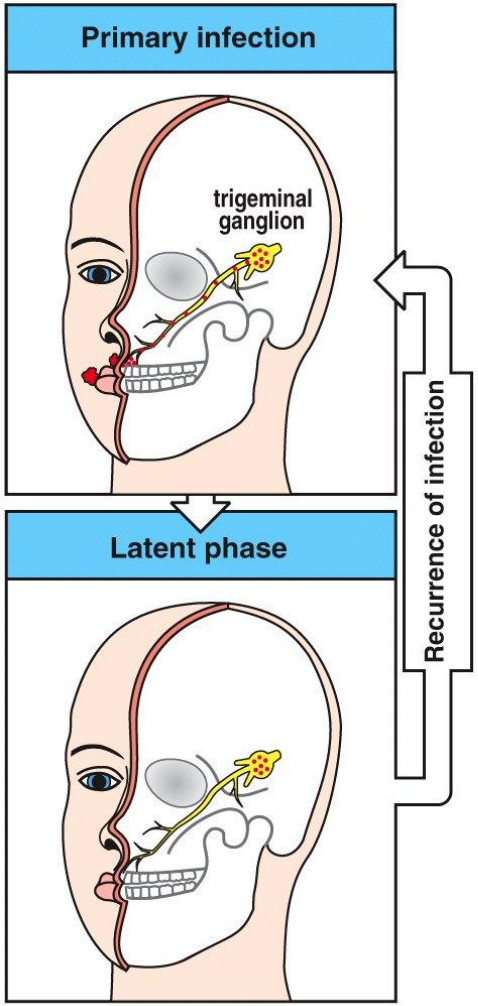


Figure 11-4 Immunobiology, 6/e. (© Garland Science 2005)

Latent viruses do not replicate, do not cause disease, and are not detected by the immune system.

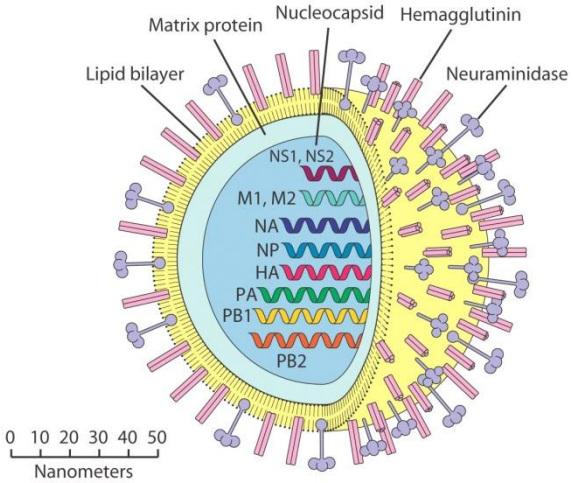
These laten viruses are activated when immune system is weakened.

Herpes simplex viruses establish latency in sensory neuron. environmental stress or decrease in immune function reactivate the virus to cause cold sores.

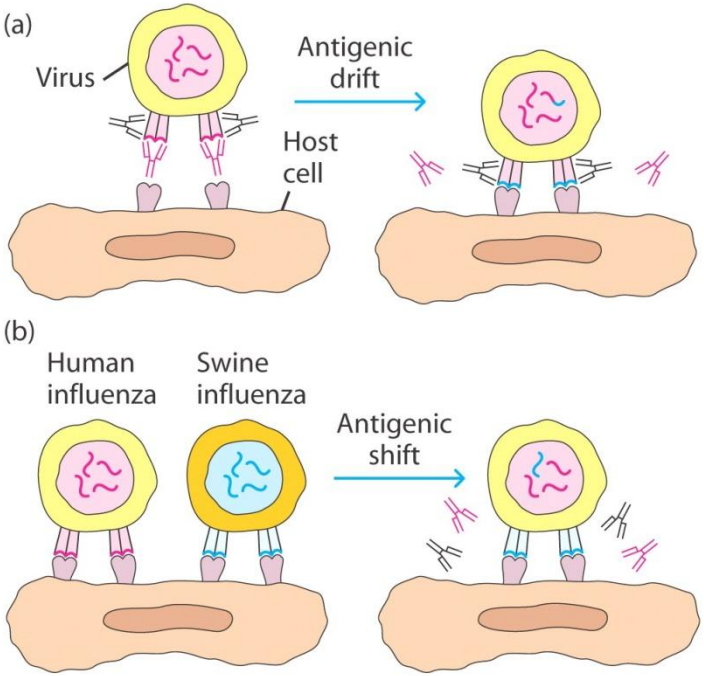
Epstein-Barr virus (EBV, herpes virus) establish latency in B cells. It produces EBNA-1, which is needed for replication. But EBNA-1 inhibits proteasome processing and antigen presentation.
Some of these infected cells can be transformed. When T cell function is compromised, they could develop into B cell lymphomas (Burkitt's lymphoma).

Mutation as evasion strategy

Influenza virus



H5N1, H1N1, etc



Evasion by hiding

Neurons produce very low levels of class I MHC.
Viruses (Rabies virus) are not effectively recognized by T cells

Destruction of Immune Cells

HIV destroyes CD4 T cells.
HBV kills CD8 effector T cells that are specific for HBV infected hepatocytes.

Interference with cytokine function

EBV, HCMV produces IL-10 like molecules to inhibit T_H1 resposne.
Some viruses express mimetics of IFN, IL2.

Downregulation of class I MHC

Inhibition of transcription, intererence with peptide transport by TAP, targeting of Newly synthesized class I MHC for degradation, and rapid turnover of surface expressed MHC.

Relevant parts in book

Interferons: p285-287
NK cells: p328-334
Viral infections: p390-395