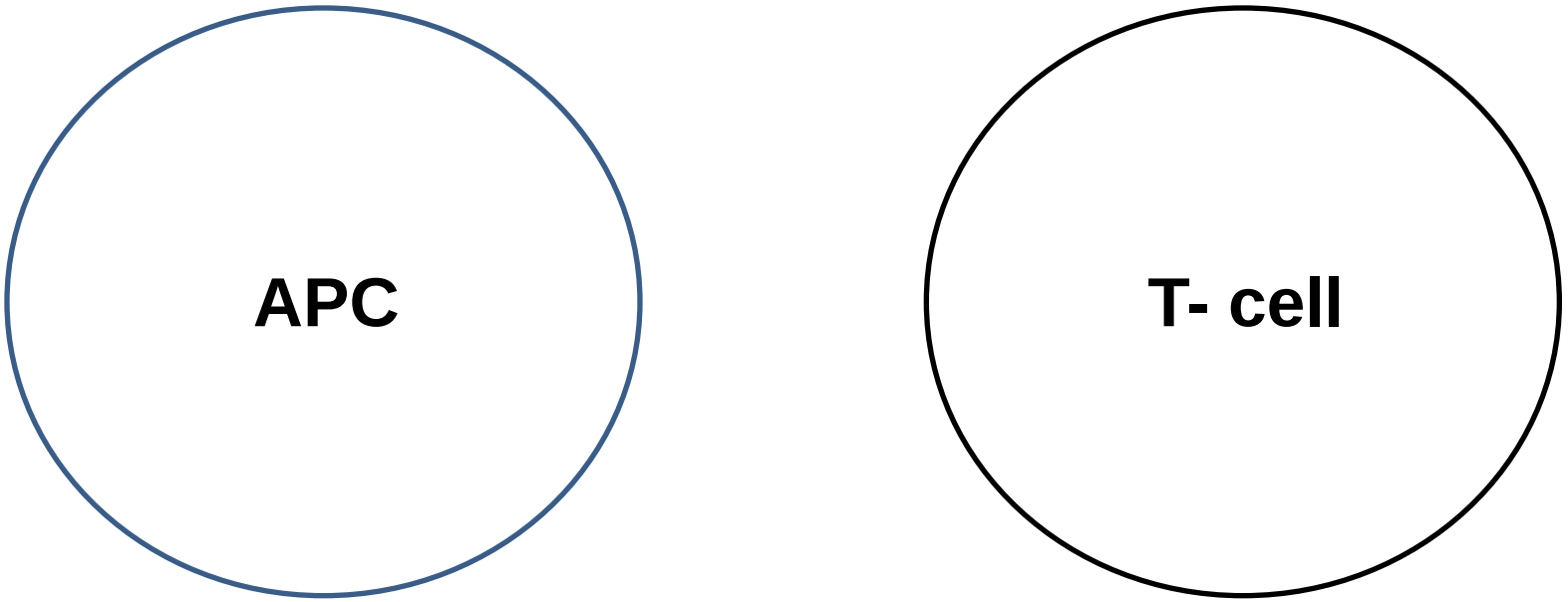
Antigen Presentation

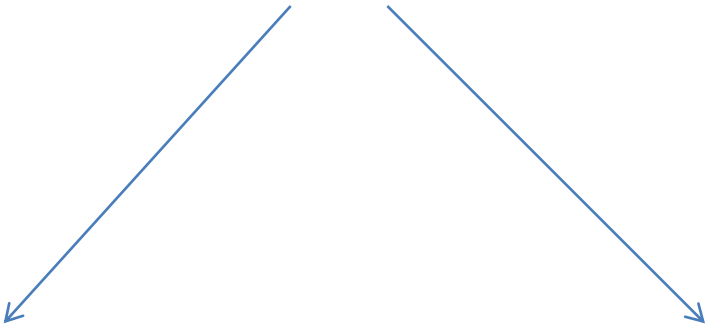
Dr. Issa Abu-Dayyeh

Antigen Presentation



What is needed to present antigen?

Major histocompatibility molecules (MHC molecules)

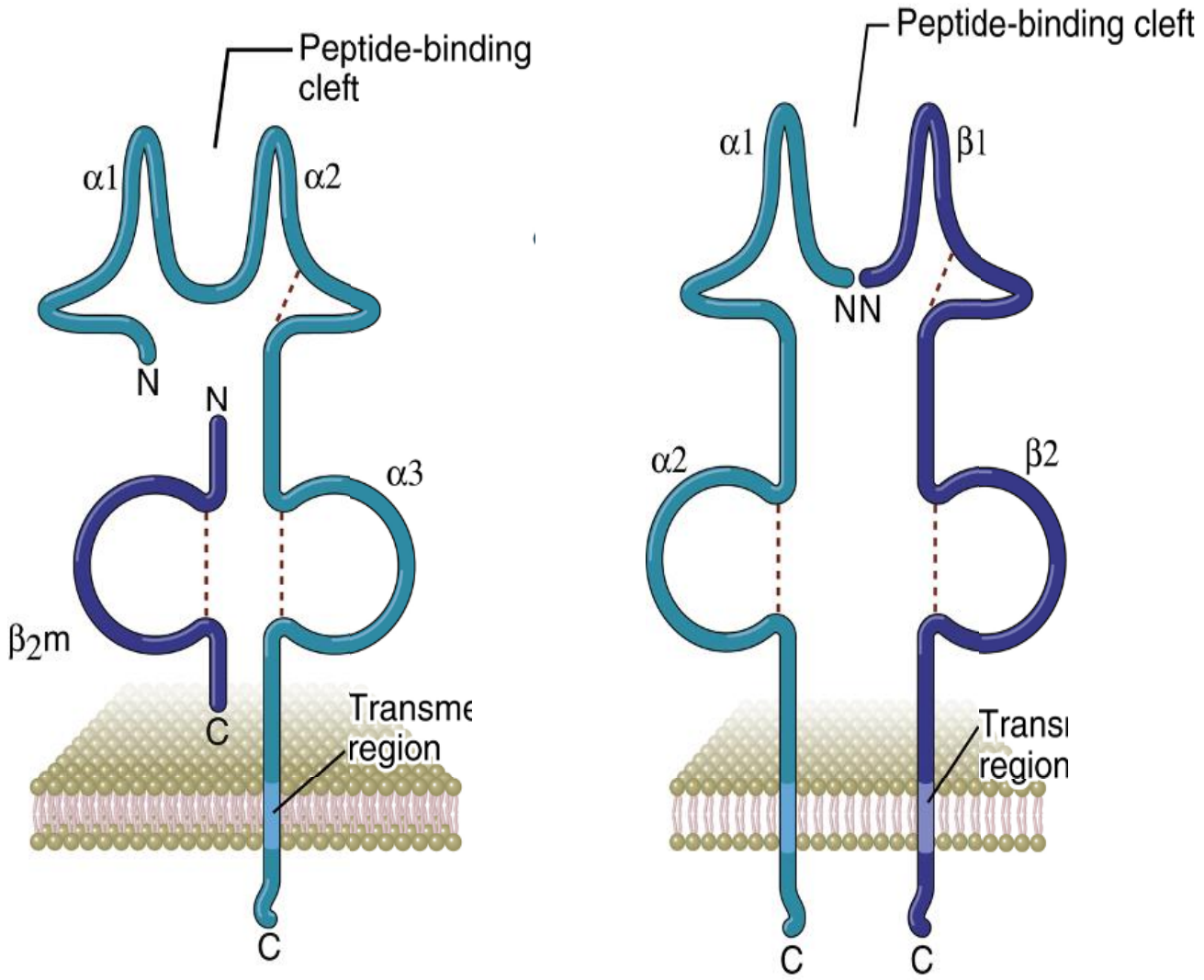


Class I MHC

Class II MHC

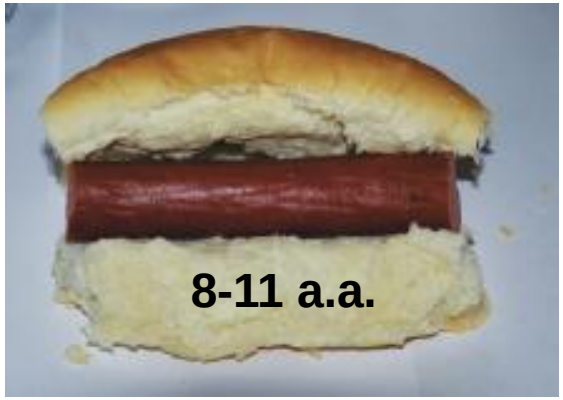
How can T cells “see” infected cells?

Antigen Presentation
By APCs.



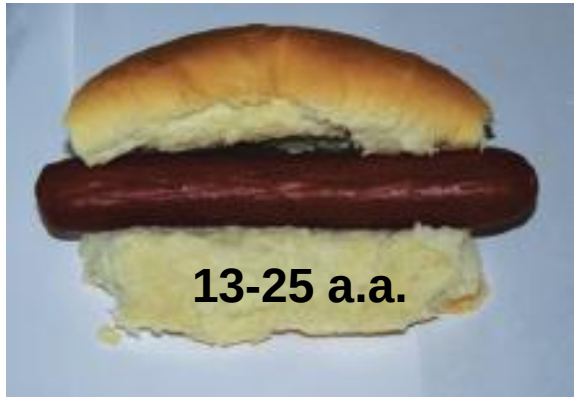
MHC I **MHC II**

Classical MHC molecules



Seen by
cytotoxic T cells

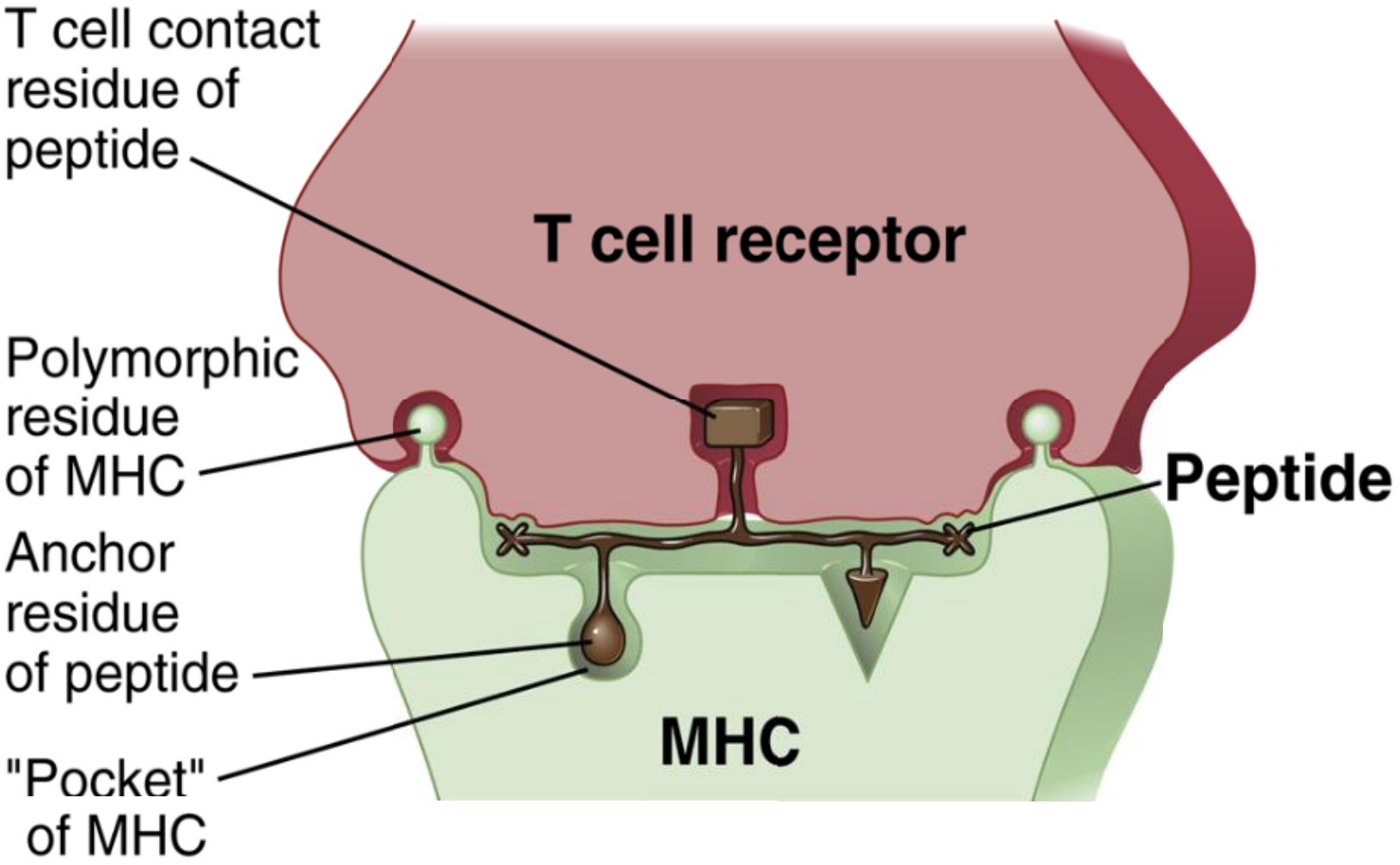
MHC class I



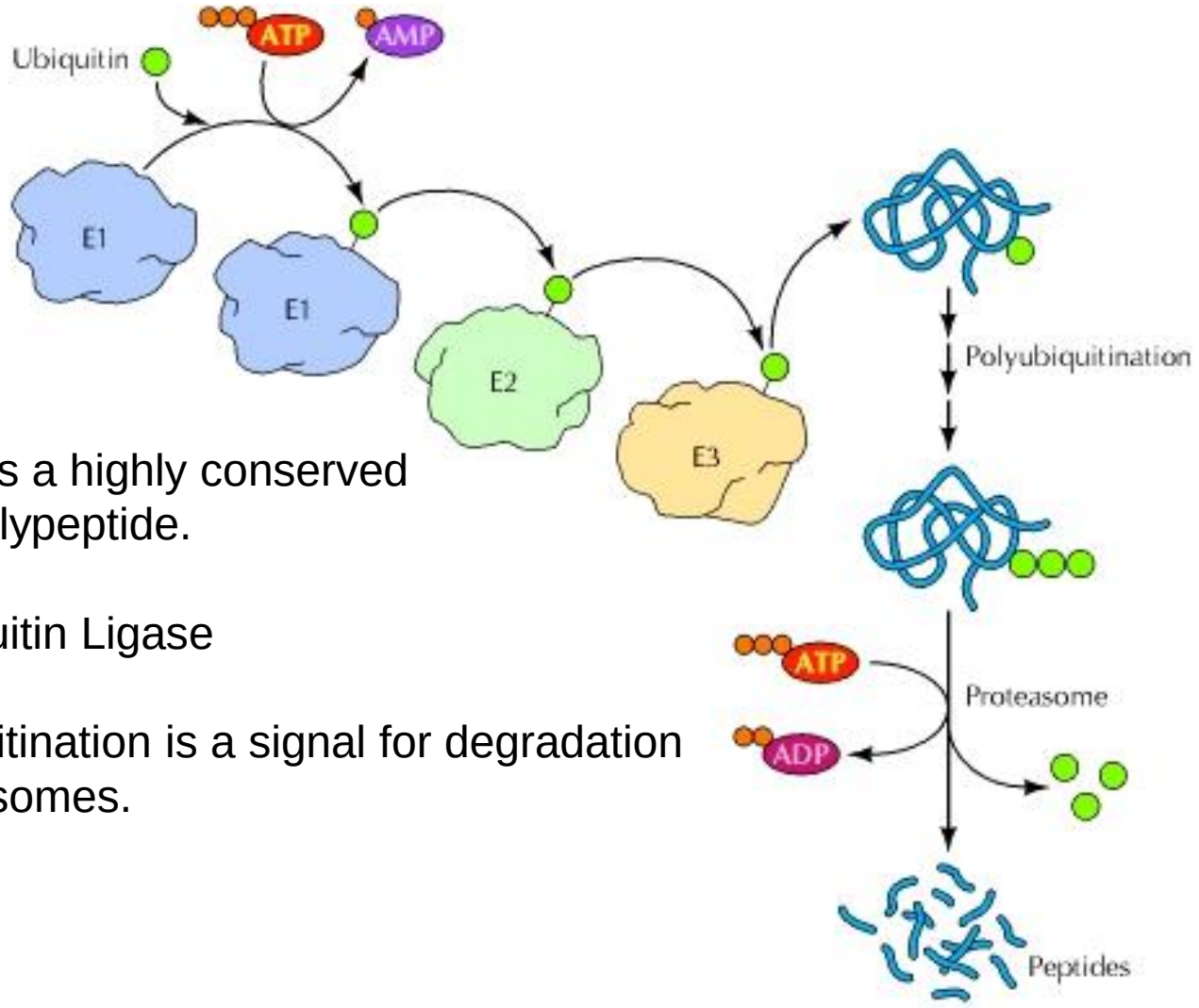
Seen by
Helper T cells

MHC class II

T-cell recognition of a peptide-MHC complex



Ubiquitin-Proteasome pathway



Ubiquitin is a highly conserved 76 a.a. polypeptide.

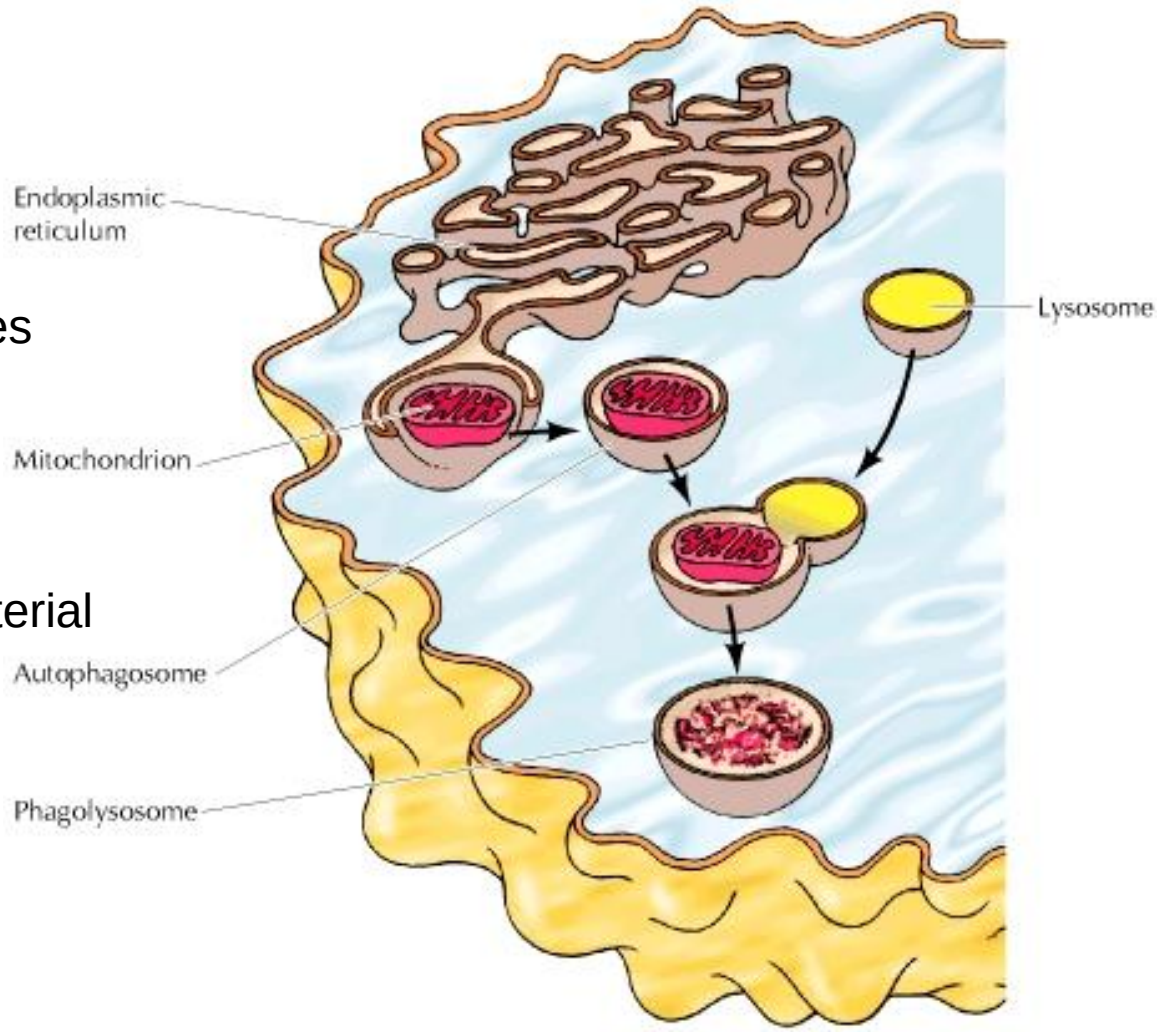
E3= Ubiquitin Ligase

Polyubiquitination is a signal for degradation by proteasomes.

Lysosomal proteolysis

Lysosomes contain proteases

Phagosomes can originate
from external or internal material



Class I MHC

Expressed on all nucleated cells.

Every human has three MHC I genes: HLA-A, HLA-B, HLA-C located on chromosome 6.

i.e. We have a total of 6 MHC I genes.

These genes are polymorphic: example, we have at least 370 variant of HLA-A and 660 variant of HLA-B. = can present variable peptide sequences.

MHC I are picky on end amino acids but flexible on central ones.

Conclusion: MHC I molecule can bind to and present a large number of different peptides, each of which fits the particular amino acids present at the ends of its binding groove.

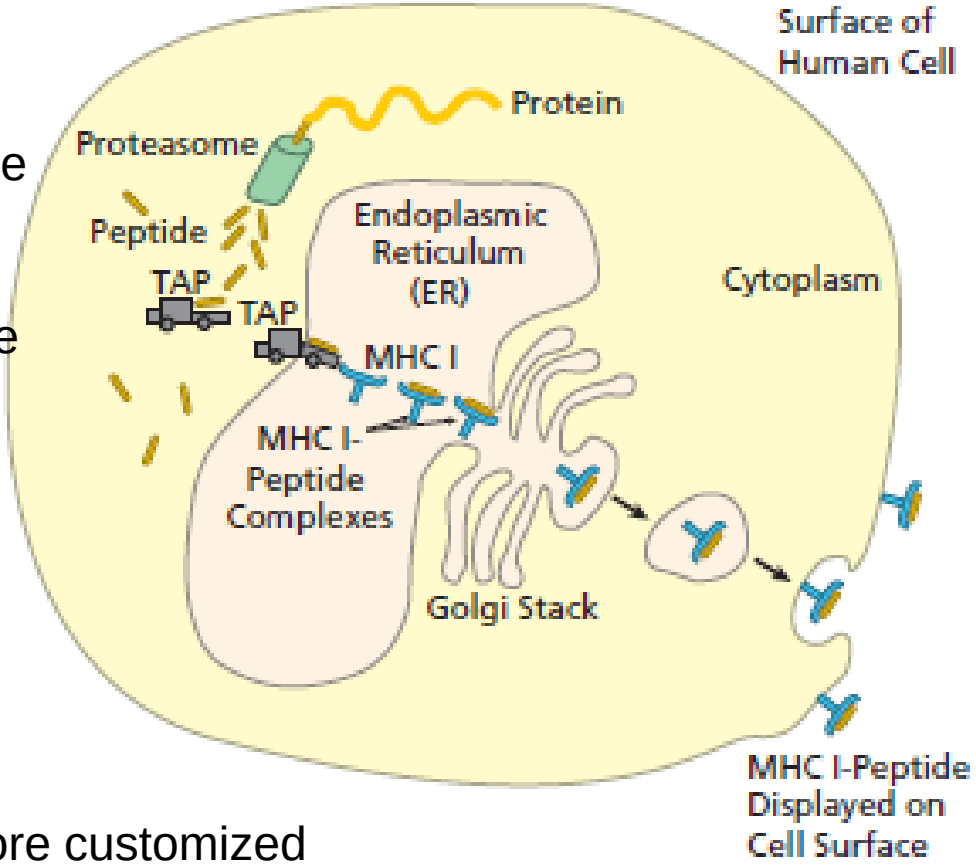
Antigen Presentation by Class I MHC Molecules

Display of proteins manufactured by the cell.

1- Generation of the peptide by the proteasome.

2- Transport of the peptide into the ER by TAP proteins. (preference To 8-15 a.a. fragments)

3-Binding of the peptide to the Groove of MHC I molecule.



Proteasome cutting process is more customized
for MHC presentation in APCs compared to non-immune cells.
(cut after hydrophobic or basic a.a. due to LMP2, LMP7, MECL-1 induced by IFN-γ)

Class II MHC

Expressed by immune cells ONLY.

Coded by HLA-D region of chromosome 6.

Highly polymorphic.

Unlike MHC I, groove is open at both ends, so peptide can hang out of the groove.

Critical peptides not at the end of the groove like MHC I, but rather spaced along it.

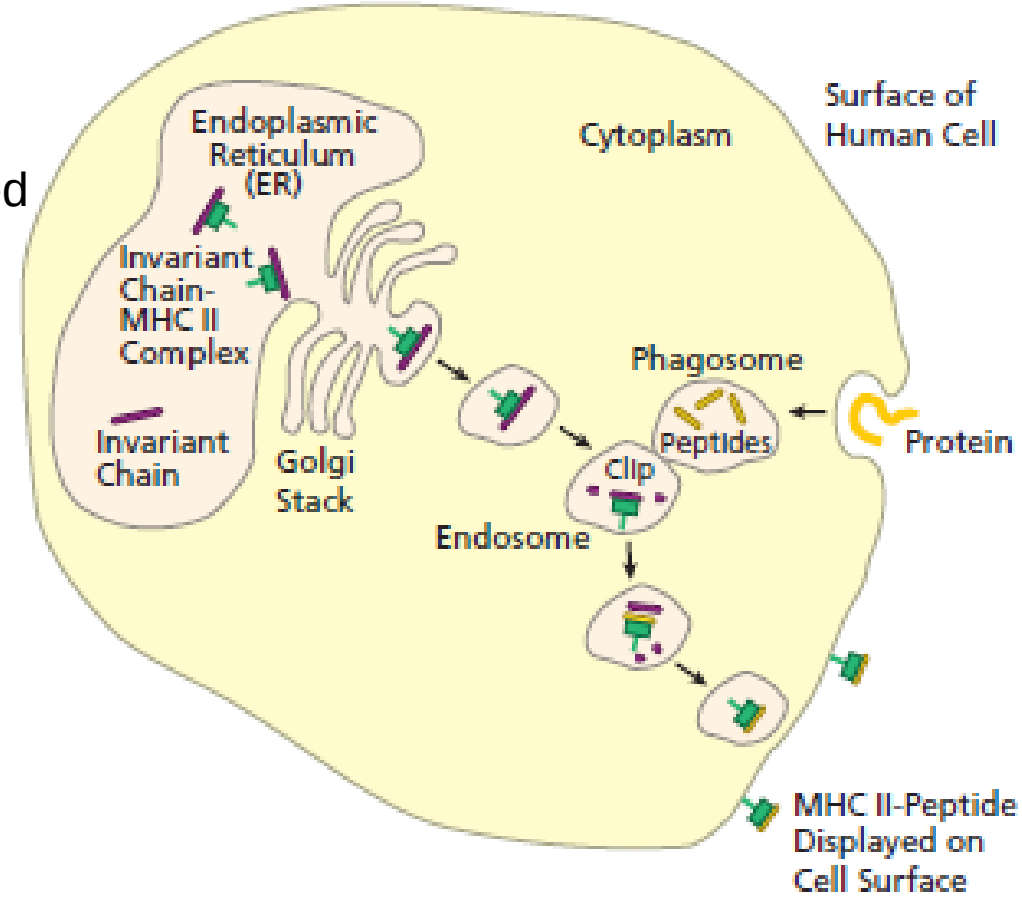
Antigen Presentation by Class II MHC Molecules

Display proteins from outside the cell.

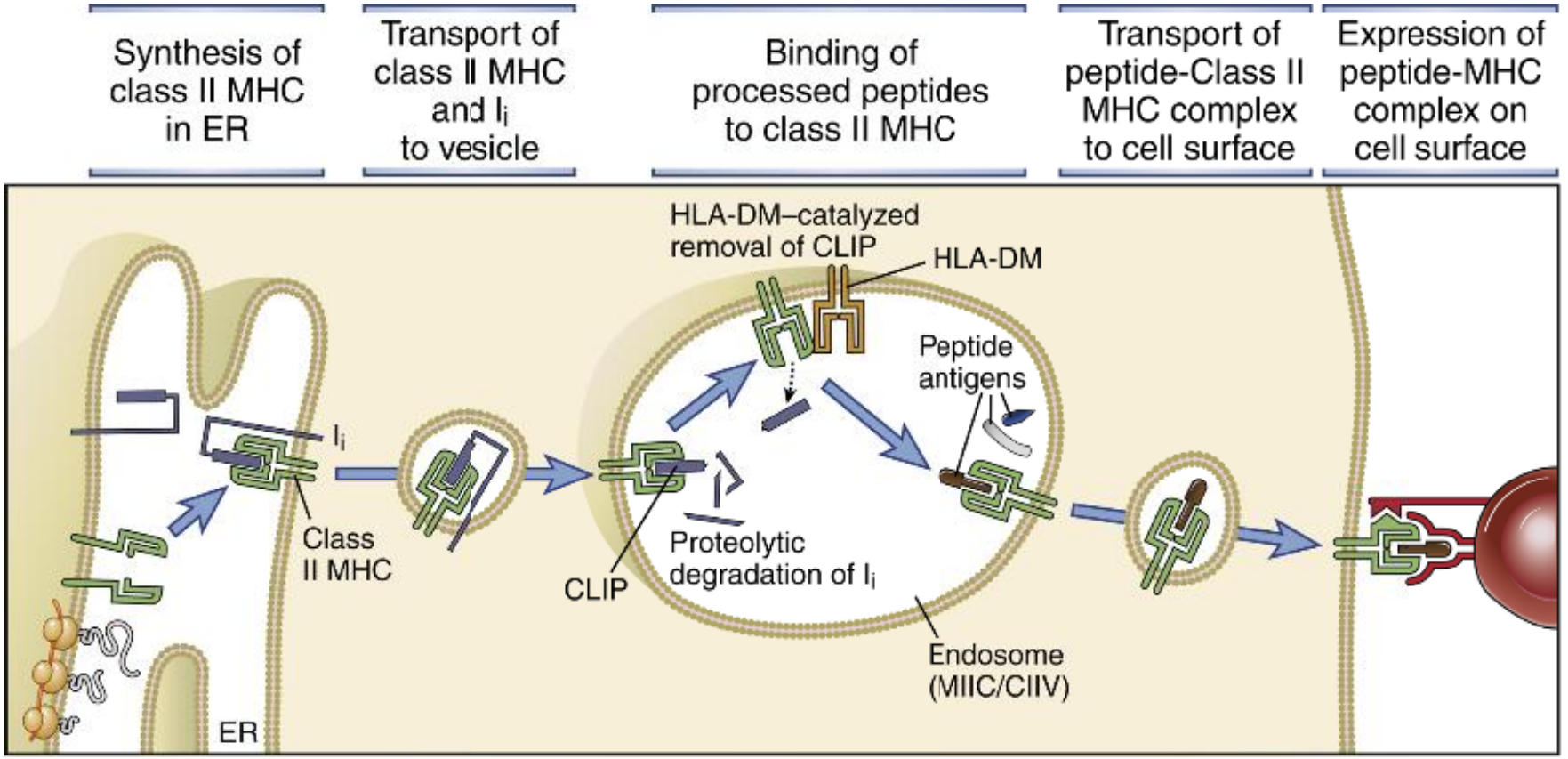
1- MHC II are synthesized and injected Into the ER where they bind to an Invariant chain.

2- Invariant chain guides MHC II from ER to endosomes.

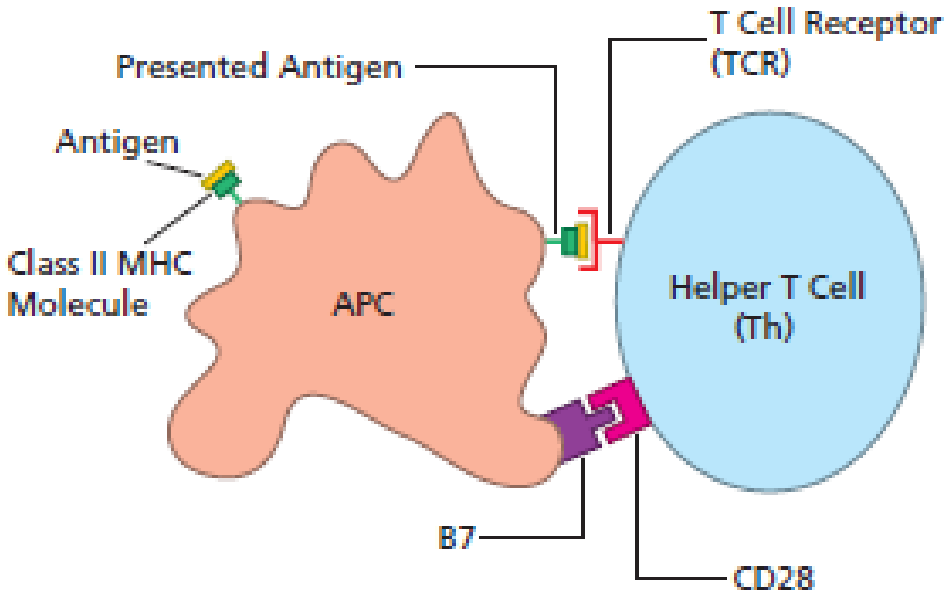
3- Endosome fuses with phagosome and exogenous peptides are loaded on the open MHC II groove.



Functions of Invariant Chain and HLA-DM

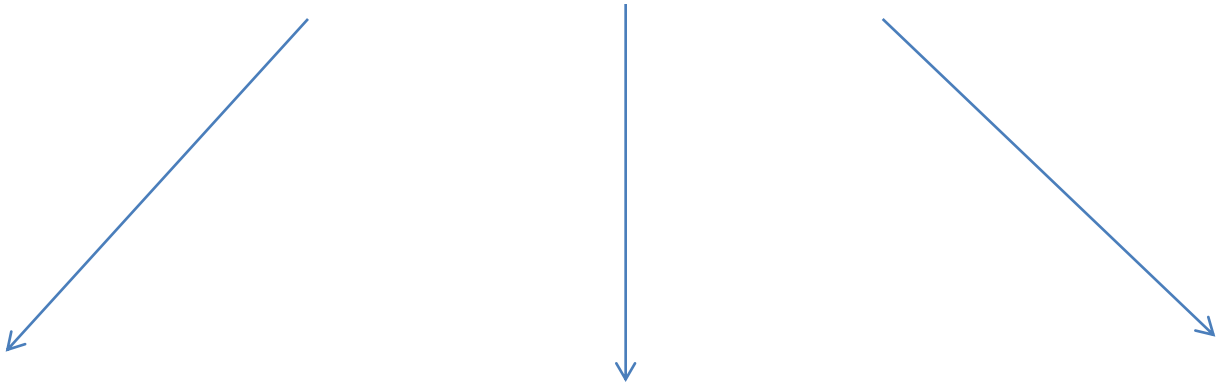


Antigen Presenting Cells (APCs)



Special cells which can provide the high levels of MHC and co-stimulatory molecules required for T cell activation.

Antigen Presenting Cells (APCs)



Dendritic Cells

Macrophages

B cells

Dendritic Cells

Starfish-like cells that can initiate the immune response by activating naive T cells.

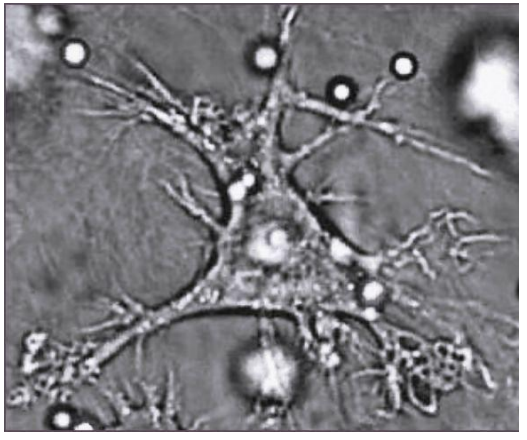
Not very good APCs in resting state, but get activated during an invasion.

Two modes of activation:

1- TNF secreted by Macrophages and neutrophils/ chemicals secreted by attacked cells.

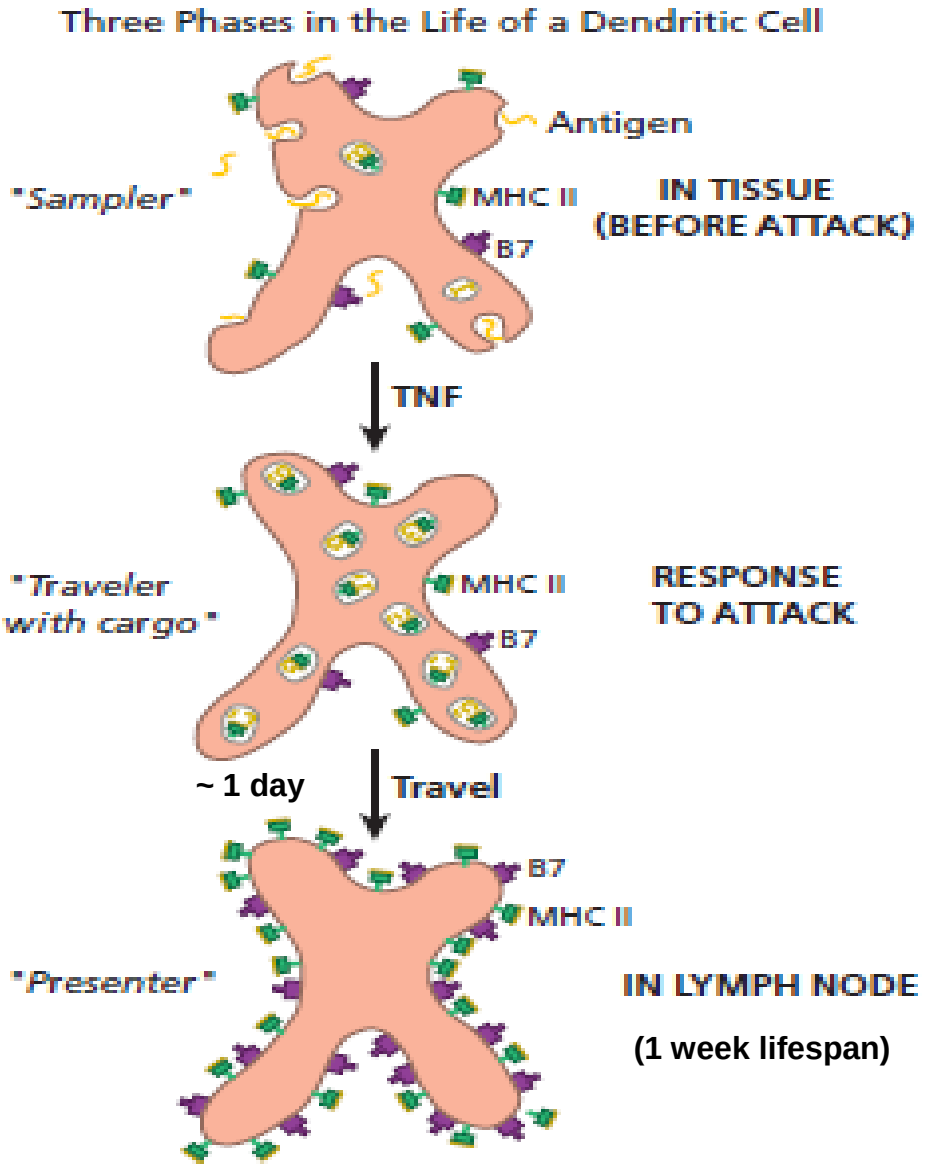
2- Toll-like Receptors (TLRs):

TLR-4: LPS (External)
TLR-7: ssRNA (Internal) HIV, influenza etc..
TLR-9: dsDNA (Internal) bacteria, HSV

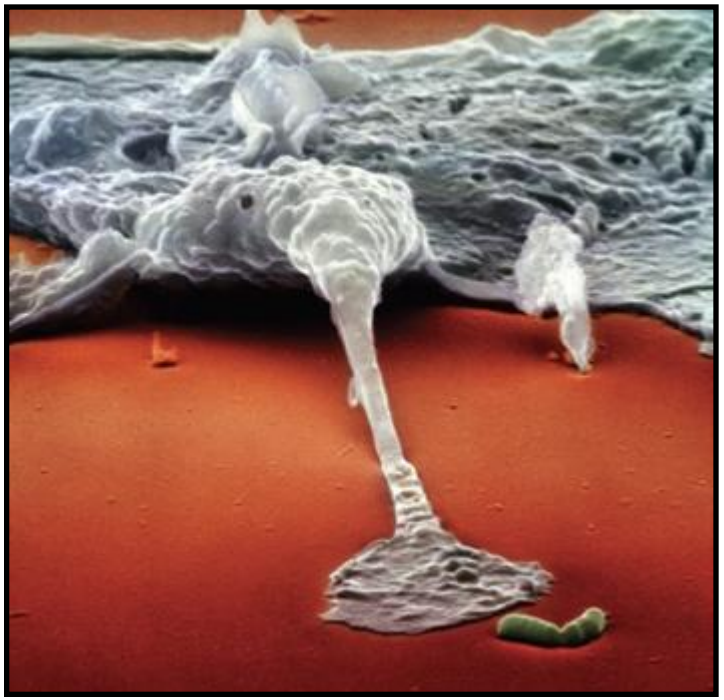


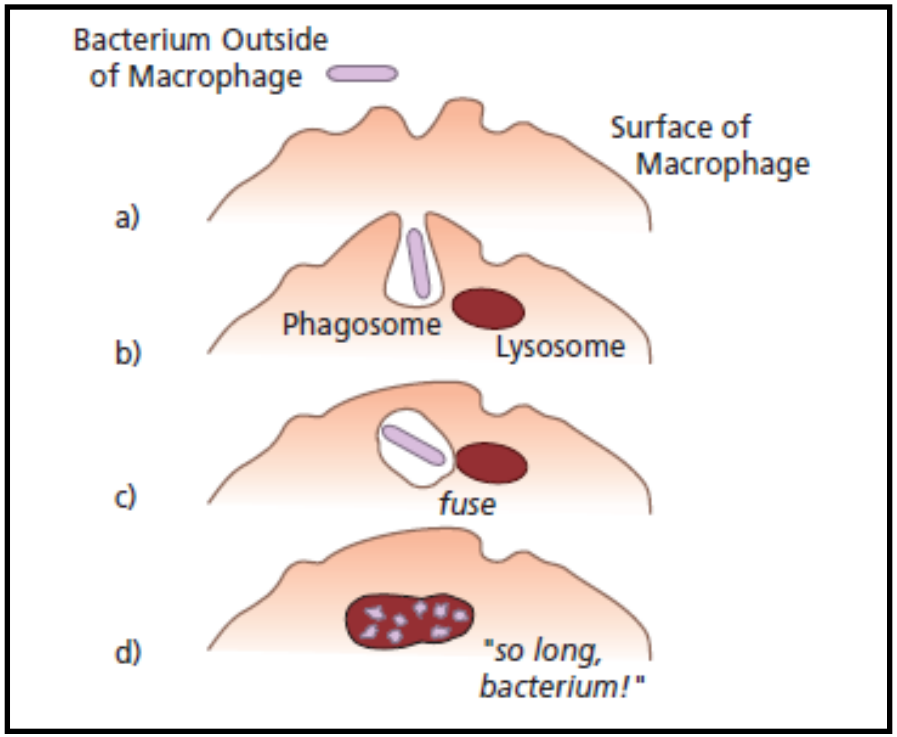
How dendritic cells work?

Send the picture from the battle field where the pathogen is located to the lymph nodes where naive T cells are located



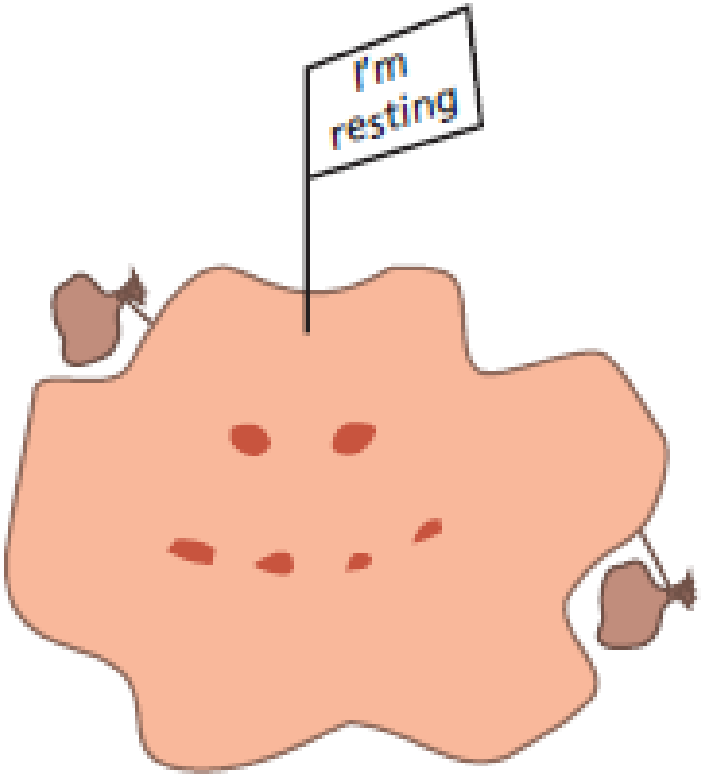
Macrophages





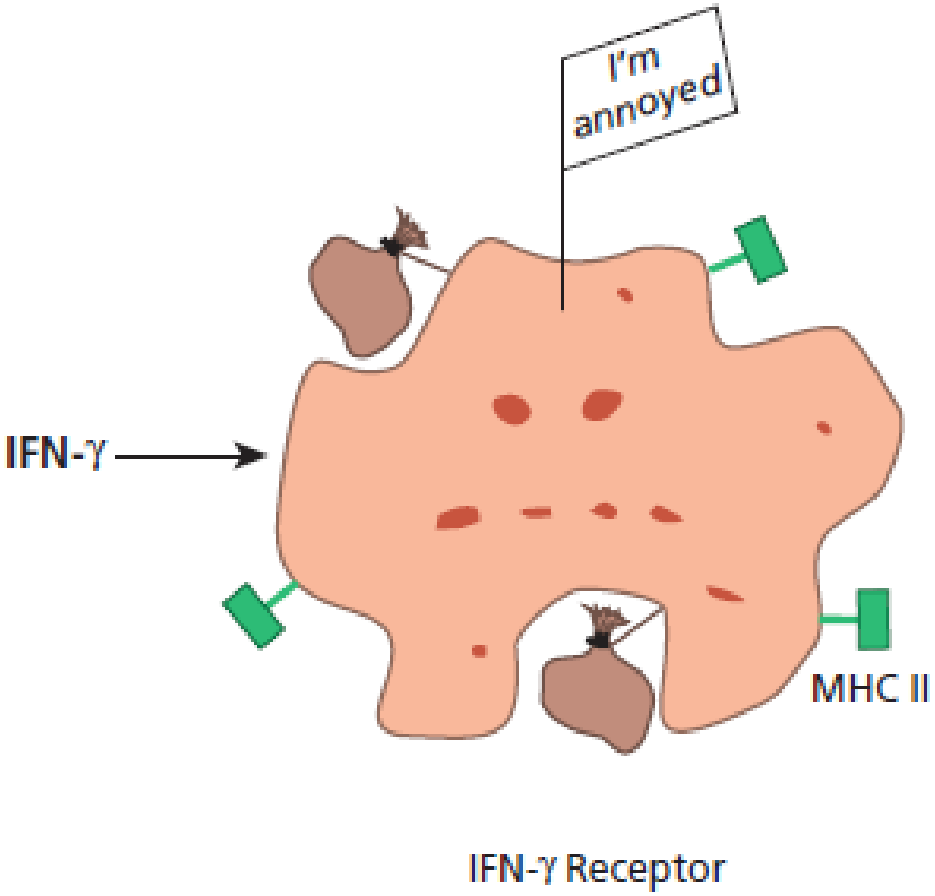
Macrophages express TLRs too!

Macrophages exist in 3 states



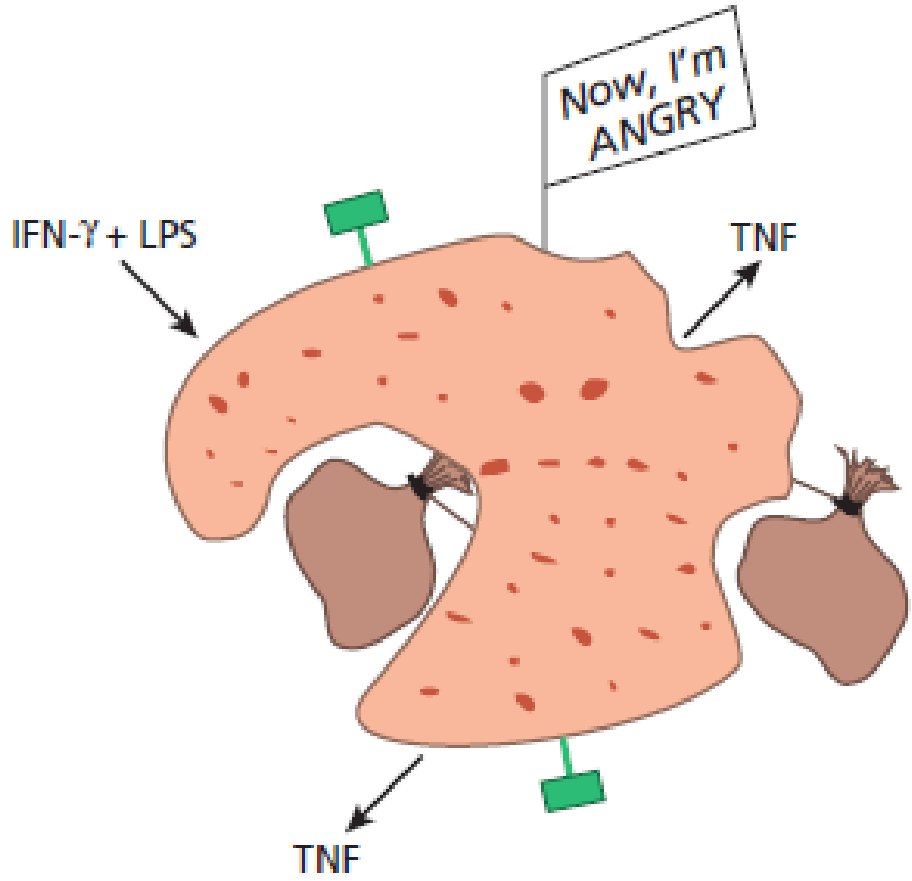
Resting Macrophage (Garbage collector)

(Low MHC II and co-stimulatory molecule expression)



Primed Macrophage (Good APC, good killer)

(up-regulate MHC II and co-stimulatory molecule expression)



Hyperactivated Macrophage (Excellent APC, highly phagocytic, more lysosomes, ROI, NO)

Unlike DCs, macrophages do not leave infected tissue to go to lymph nodes.

How can they serve as APC???

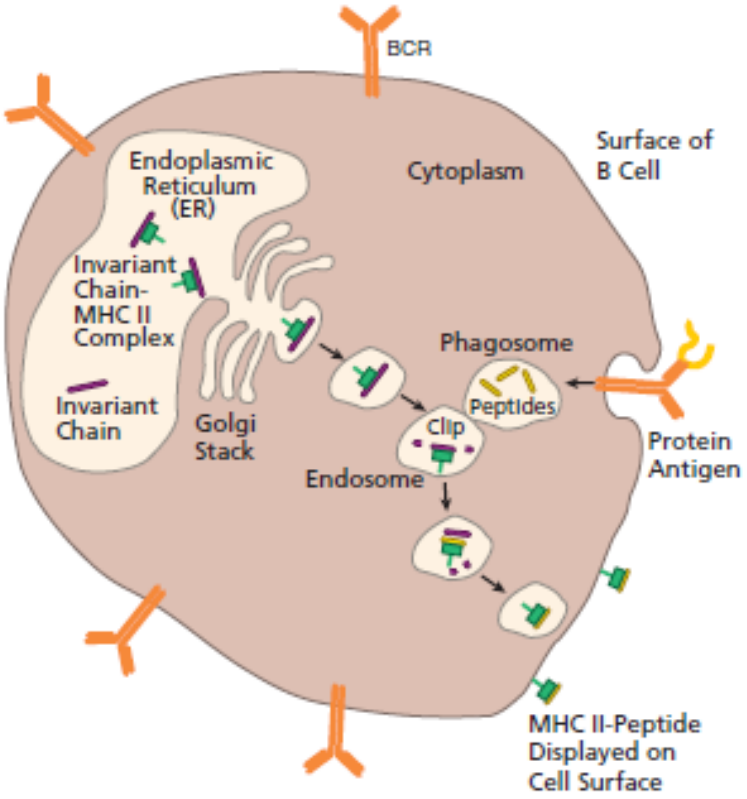
B cells

Activated later in the course of infection or in subsequent infections by Th.

Once activated B cells can act as APCs for naive Th cells.

Unlike other APCs, B cells can concentrate Ag for presentation using their BCRs.

When little Ag around, B cells are 100-10,000 fold better as an APC compared to DCs and macrophages.



The logic of MHC presentation

Why bother with antigen presentation at all??

Why bother with Class I presentation?

Focuses the attention of killer T cells on infected cells not on pathogens outside cells. Anything outside cells can be dealt with by antibodies and phagocytes.

Without Class I system, any pathogenic Ag stuck to a surface of an innocent cell could trigger T cell killing.

This system allows display of pathogen proteins that are inside the cells which would normally never make it to the the cell surface.

MHC I requires proteins to be chopped into short pieces exposing hidden epitopes to killer T cells.

Why bother with class II presentation?

Many pathogens do **NOT** infect human cells, infecting tissue and blood.
MHC II system samples the outside environment and alerts Th cells.

MHC II restriction requires that APC and Th cell agree there is danger. Adaptive response decision is **NOT** made by a **SINGLE** cell.

MHC II system requires antigens to be chopped to smaller pieces allowing more Th cells to recognize the antigen and mount a more efficient response.

Why are MHC molecules so polymorphic??

Why 6 MHC I genes?

Suppose a pathogen mutates in a way where its peptides cannot bind a single MHC I molecule! More MHC molecules..better chance of being able to present mutated antigen. (HIV patients with 6 MHC I genes live longer than those with fewer genes)

MHC proteins and organ transplants

In the 1930s, it was observed that tumor cells could only be transplanted from one mouse to the other when they are from the same inbred strain.

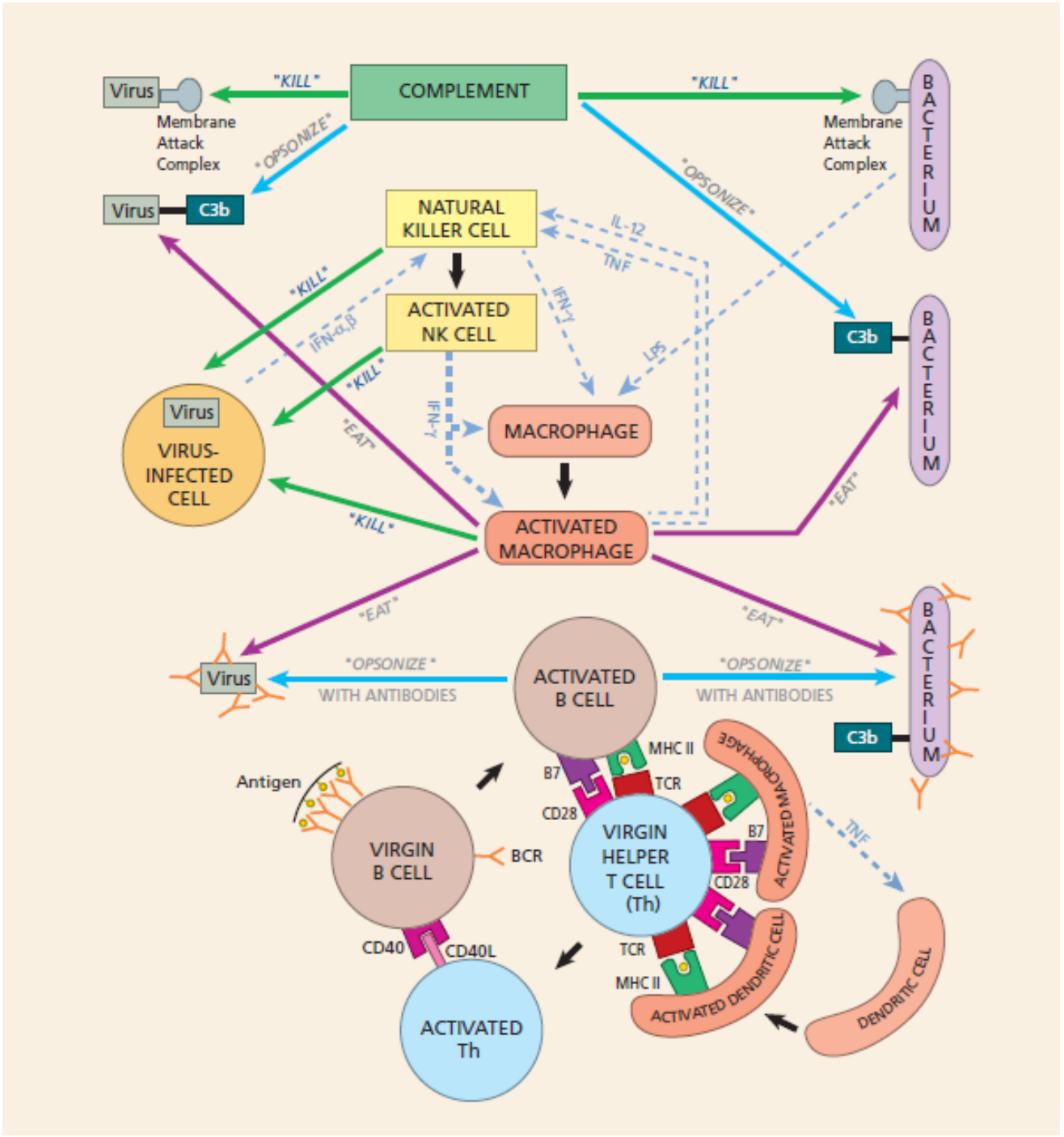
Similar observations was seen in skin grafts between mice. (MHC are implicated in tissue compatibility.

MHC molecules used in Ag presentation, are the very same molecules responsible for immediate rejection of transplanted organs.

Killer T cells attack foreign MHC, cells lining blood vessels of tissues dye cutting blood supply to transplanted organ.

MHC matching concept (Donor and recipient)

To find a class I and II compatible person (non-relative): You need to scan 10,000,000 different people for a 50% chance!


Virus
"KILL"
COMPLEMENT
"KILL"
BACTERIUM
Membrane Attack Complex
"OPSONIZE"
Membrane Attack Complex
Virus
C3b
"OPSONIZE"
NATURAL KILLER CELL
IL-12
TNF
"KILL"
IFN-α,β
IFN-γ
ACTIVATED NK CELL
C3b
BACTERIUM
LPS
"KILL"
Virus
VIRUS-INFECTED CELL
IFN-γ
MACROPHAGE
"EAT"
"KILL"
ACTIVATED MACROPHAGE
"EAT"
"EAT"
"EAT"
BACTERIUM
Virus
"OPSONIZE" WITH ANTIBODIES
ACTIVATED B CELL
"OPSONIZE" WITH ANTIBODIES
C3b
MHC II
B7
TCR
CD28
Antigen
VIRGIN B CELL
BCR
VIRGIN HELPER T CELL (Th)
B7
CD28
ACTIVATED MACROPHAGE
TNF
CD40
CD40L
TCR
MHC II
ACTIVATED DENDRITIC CELL
DENDRITIC CELL
ACTIVATED Th

Thank you!

Questions???