Antigen presentation

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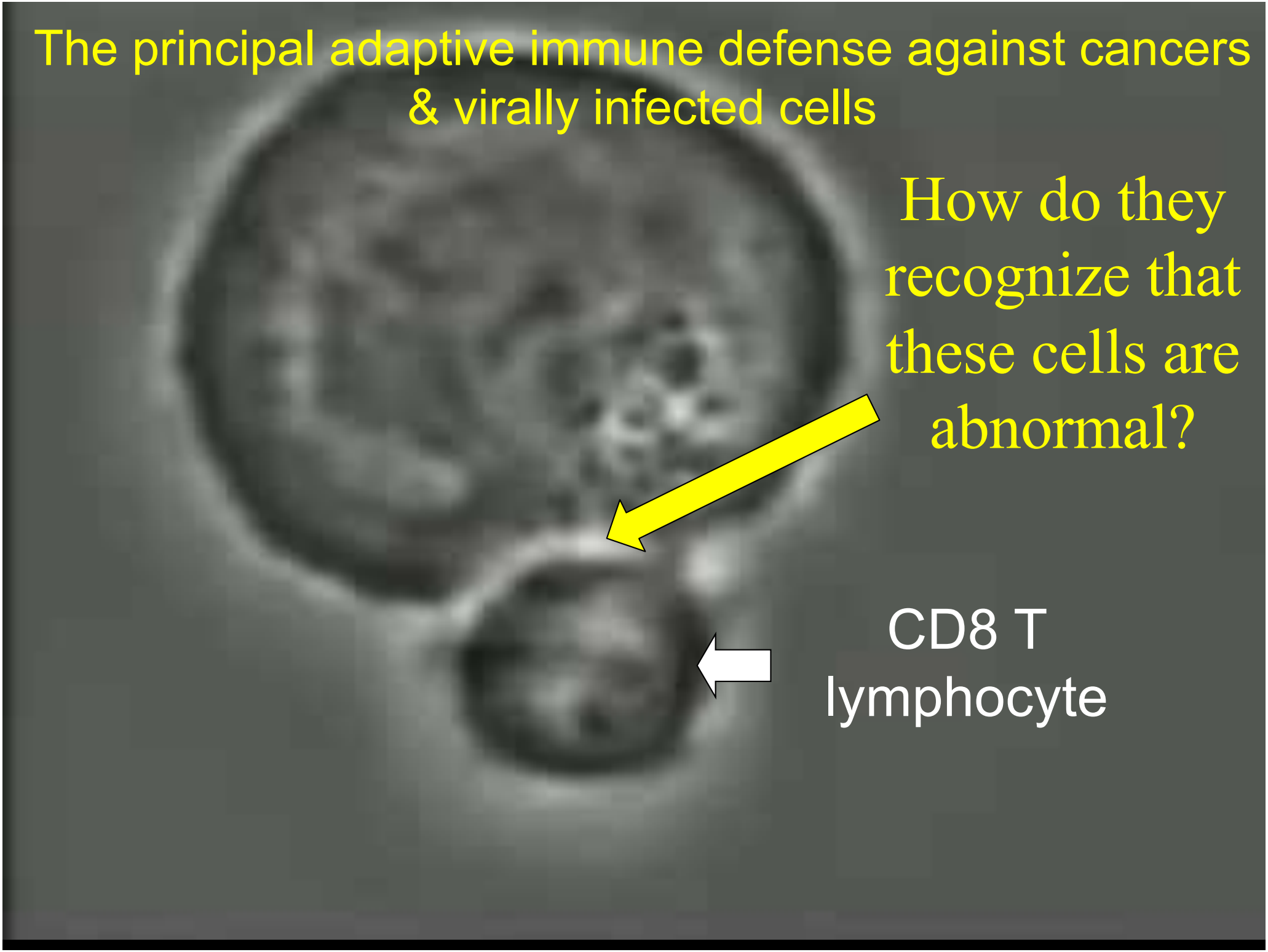
UMass Medical School

Lecture outline

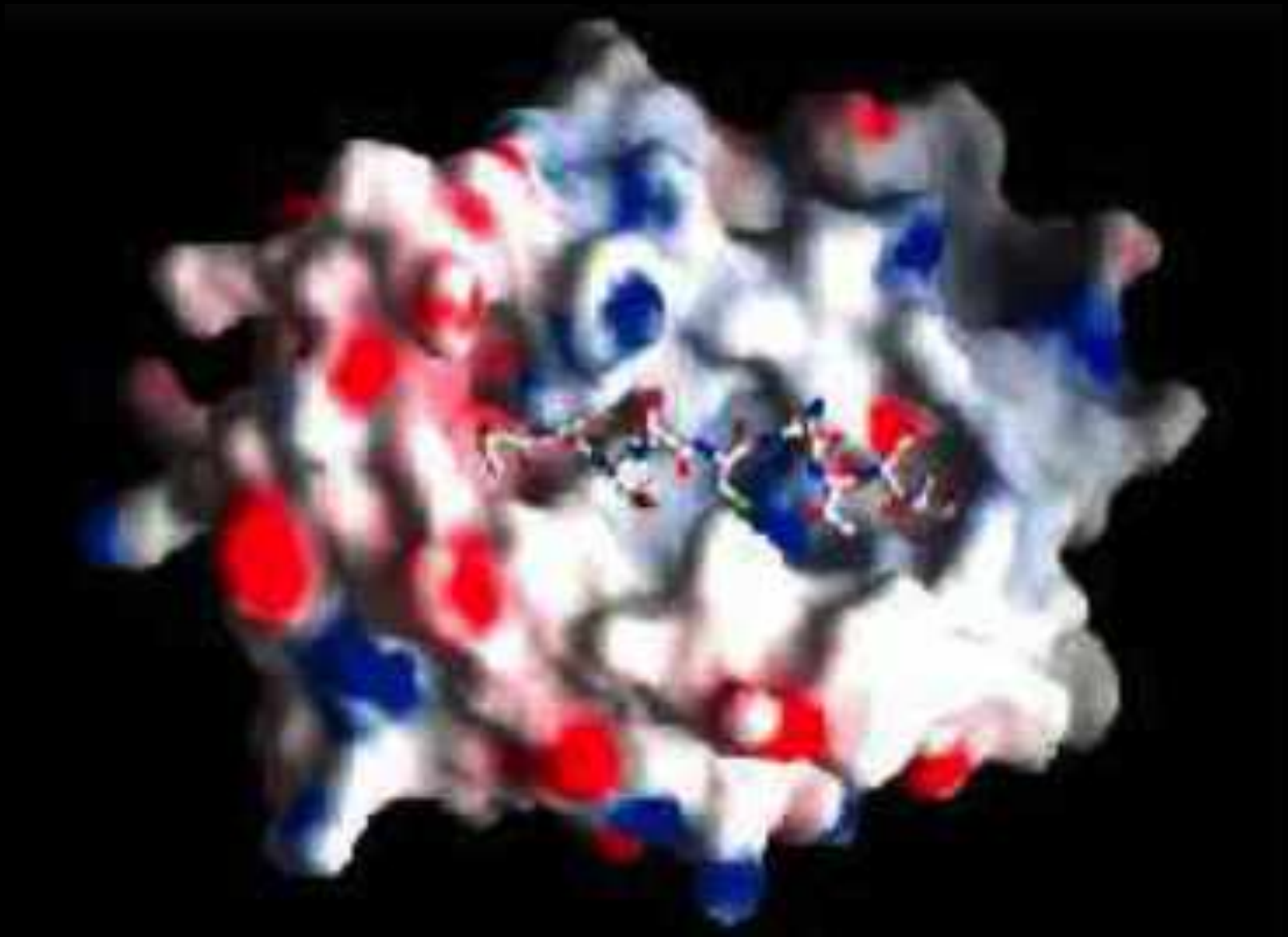
MHC I Ag presentation

MHC II Ag presentation

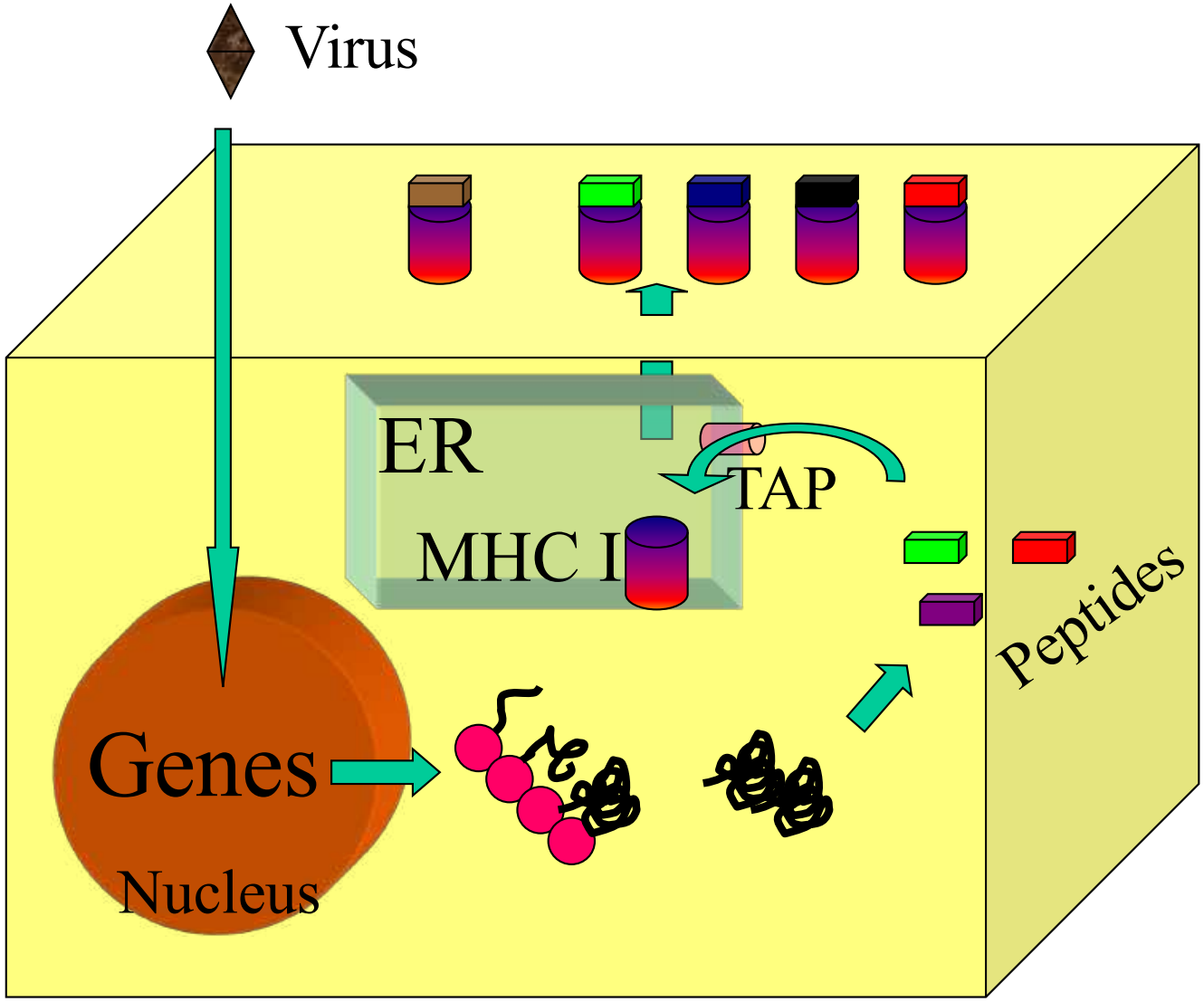
Dendritic cells & Cross-presentation (if time)


The principal adaptive immune defense against cancers & virally infected cells
How do they recognize that these cells are abnormal?
CD8 T lymphocyte

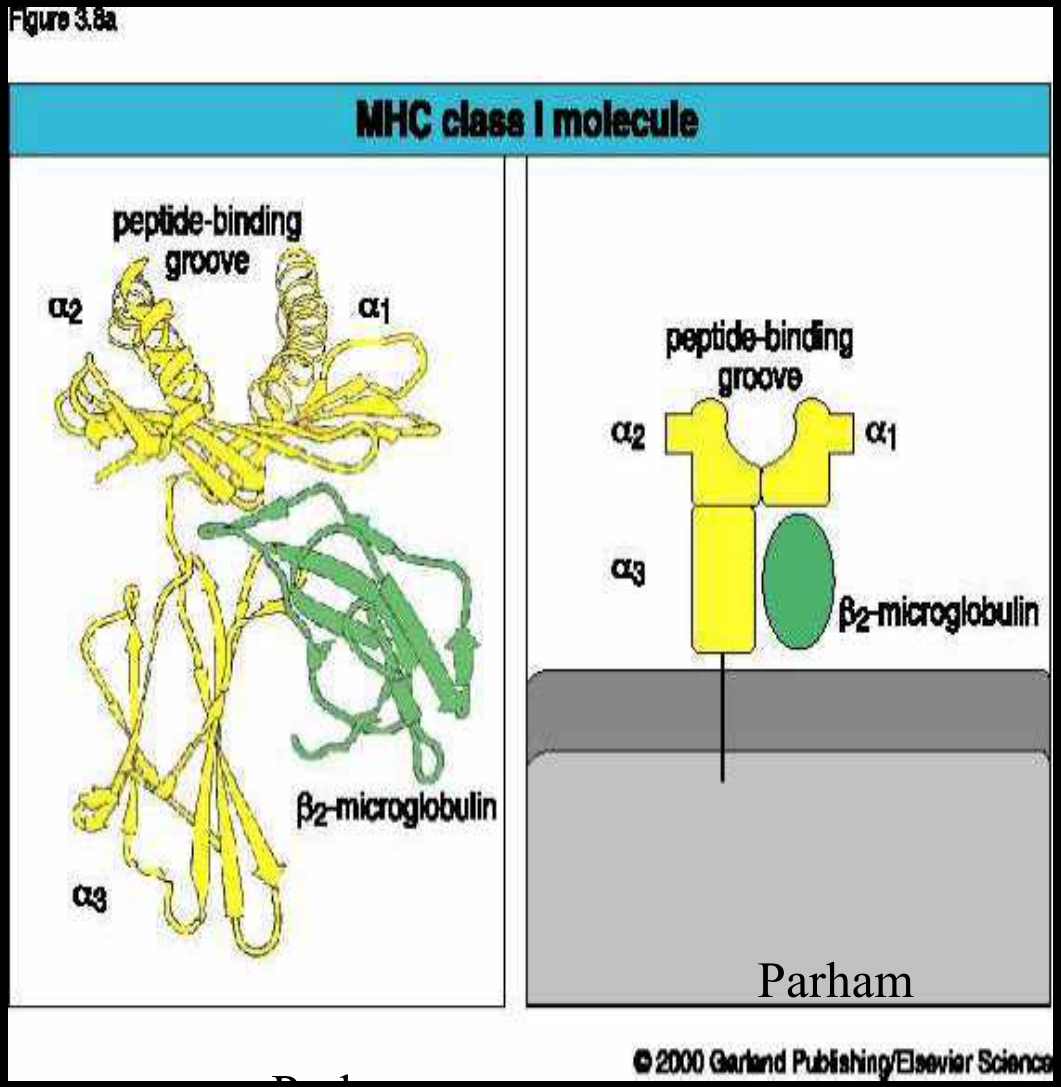
MHC class I molecule



MHC class I antigen presentation



The MHC I antigen binding receptor



From Kuby

MHC class I genes

Mouse H-2 complex

Complex	H-2						Tla	
MHC class	I	II		III		I	I	I
Region	K	IA	IE	S		D	Qa	Tla
Gene products	H-2K	IA αβ	IE αβ	C′ proteins	TNF-α TNF-β	H-2D	H-2L	Qa	Tla, Qa

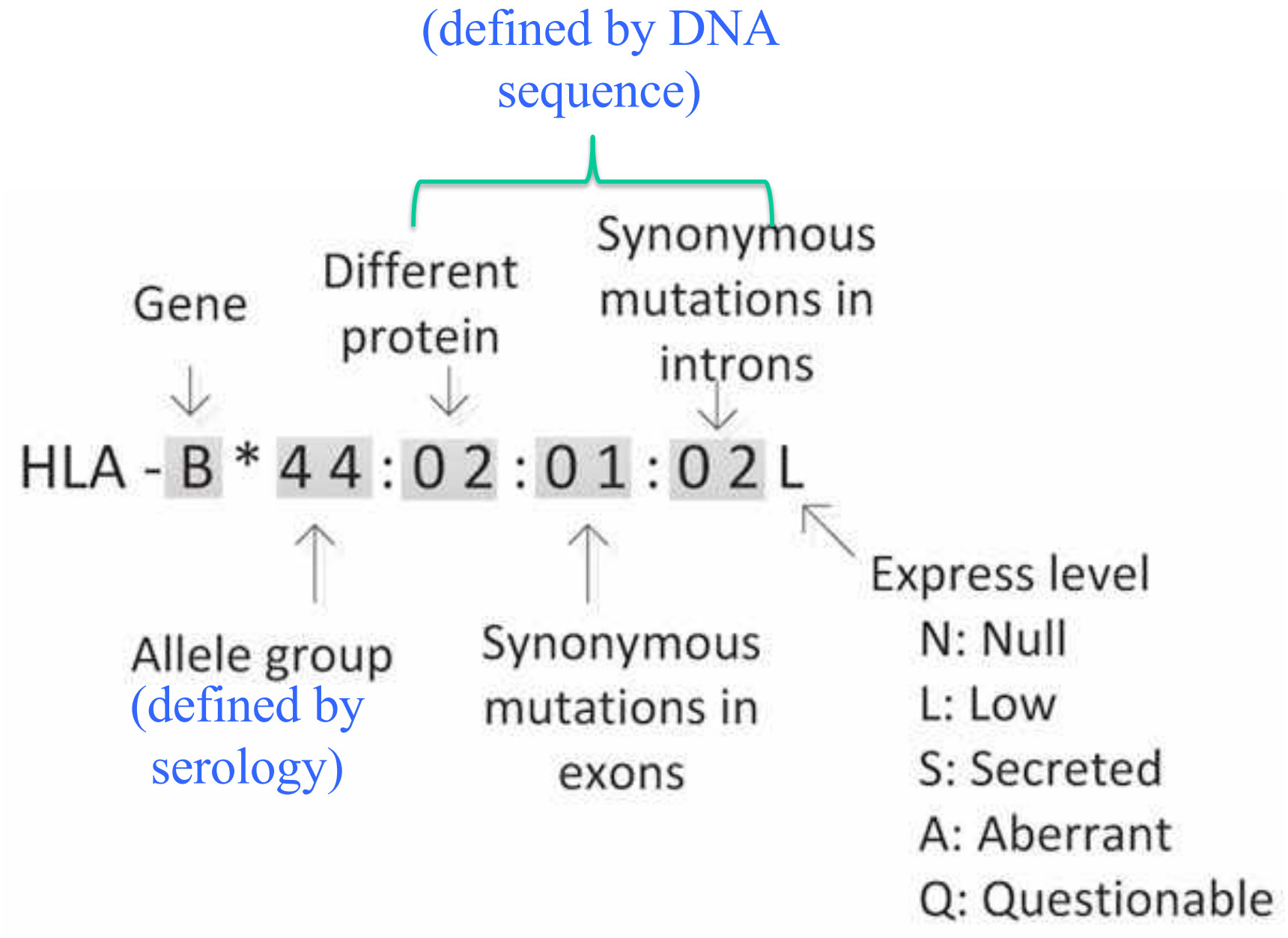
Human HLA complex

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

MHC class I genes are highly polymorphic

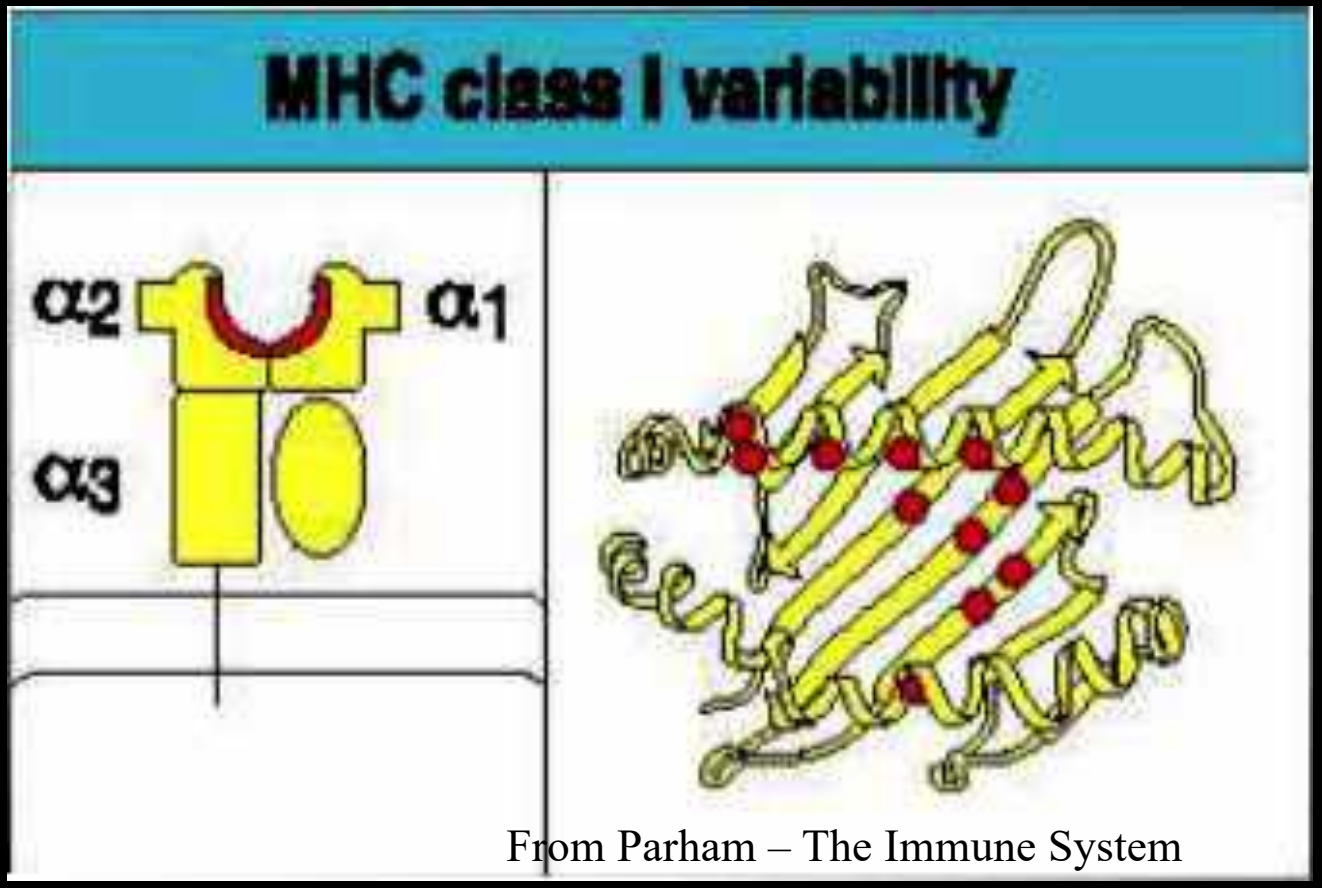
Now >10,000 alleles of MHC class I genes identified!!

Nomenclature



MHC Class I genes are highly polymorphic

Where are the polymorphic residues?



From Parham – The Immune System

What will the polymorphisms affect?

Clinical importance of MHC polymorphism

Transplant rejection

Susceptibility to infectious disease (e.g. HIV elite controller)

Susceptibility to autoimmune disease

Responses to vaccines & immunotherapy

MHC I molecules –Expressed all (A,B,C) co-dominantly (both chromosomes)

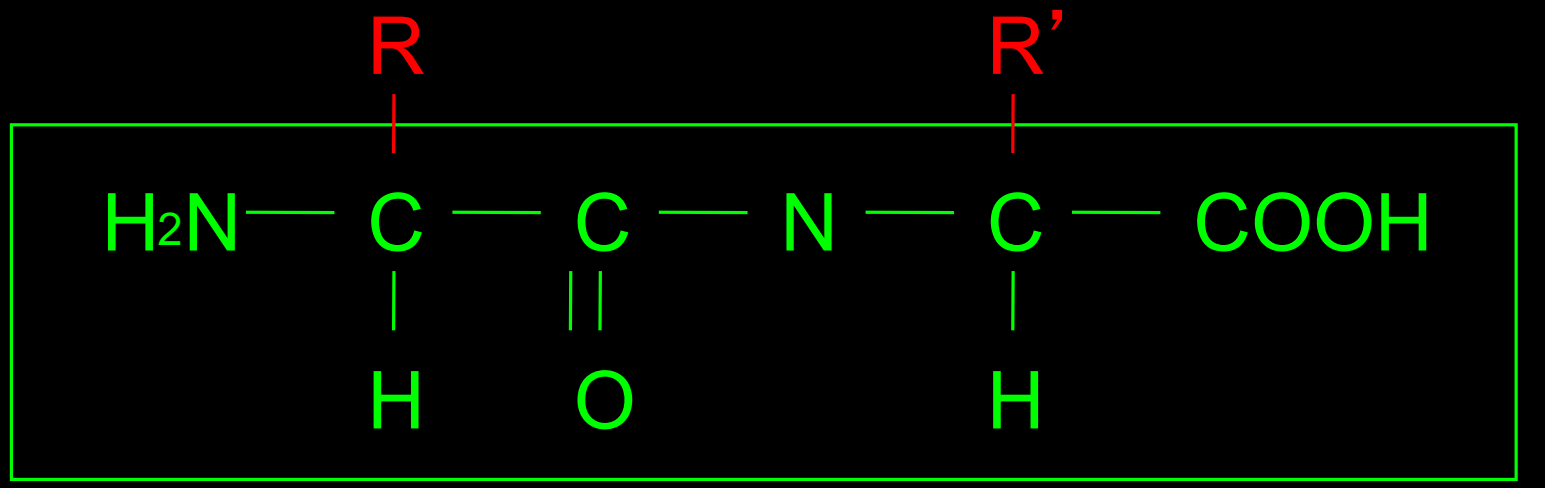
How many different MHC I molecules can cells express?

How can ≤ 6 MHC I molecules present all Antigens?

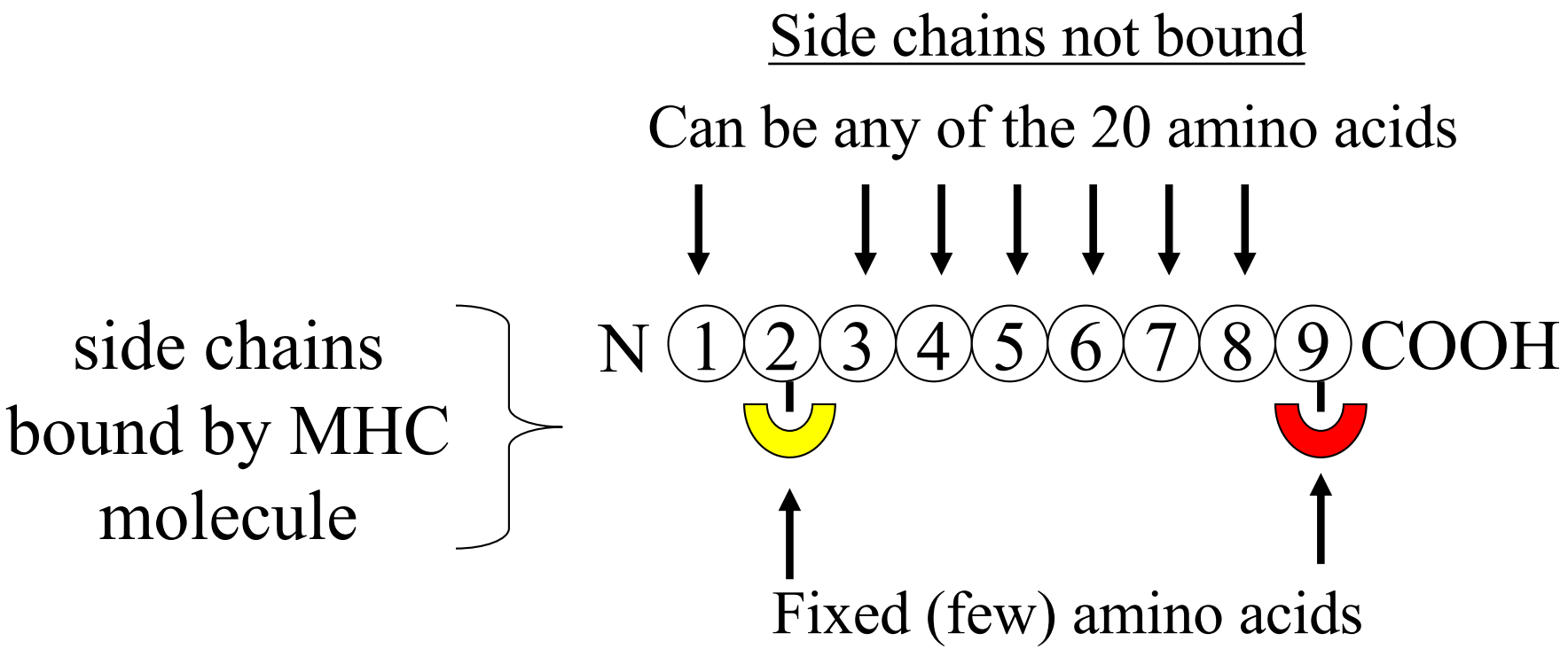
Peptide Structure

Unique

Common



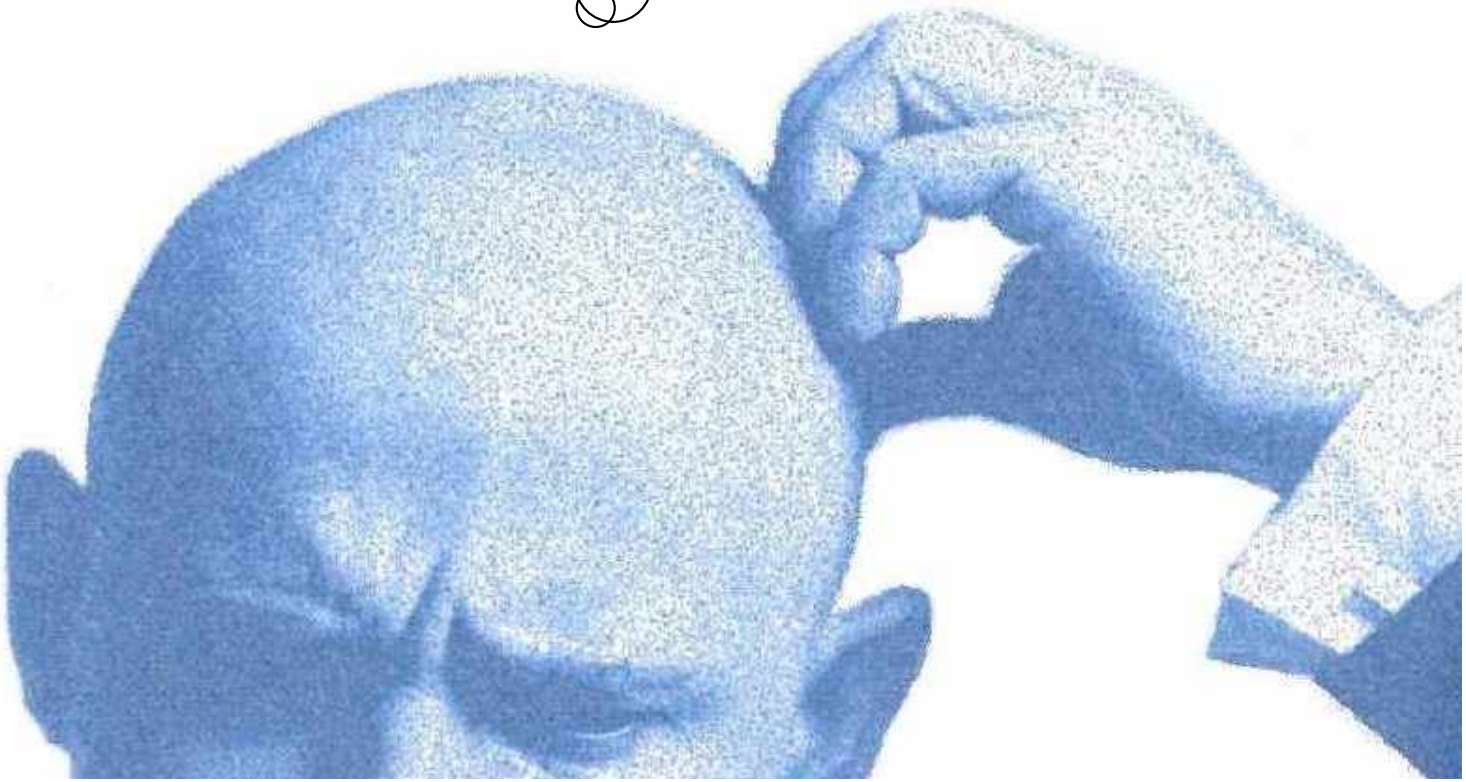
Peptides bound to MHC molecules



Therefore, a single MHC I molecule can bind huge numbers of peptides (but not all)

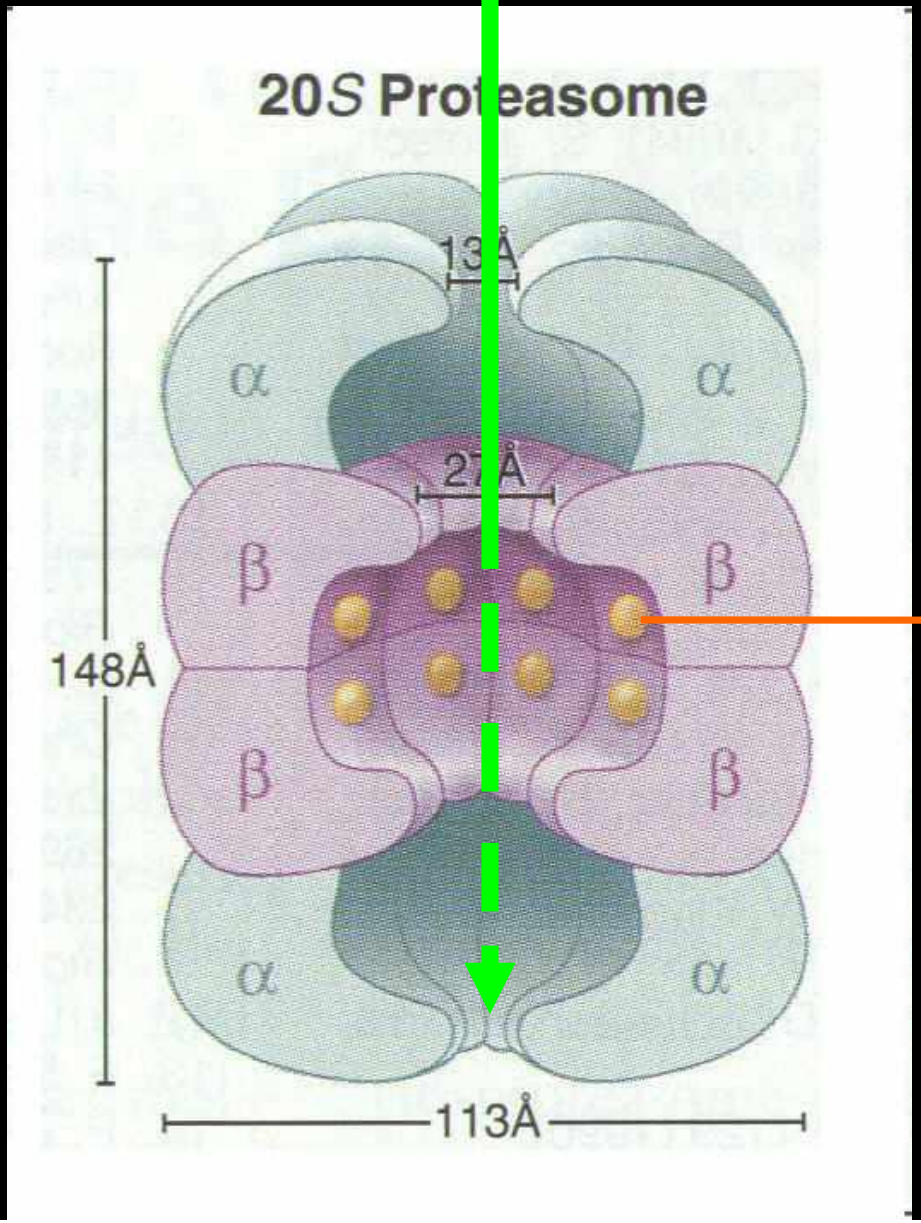
With 6 different MHC I molecules, can "cover" much of the antigenic universe

So, how do we get from proteins to presented peptides



MHC class I pathway utilizes the peptides generated from the normal catabolism of cytosolic & nuclear proteins

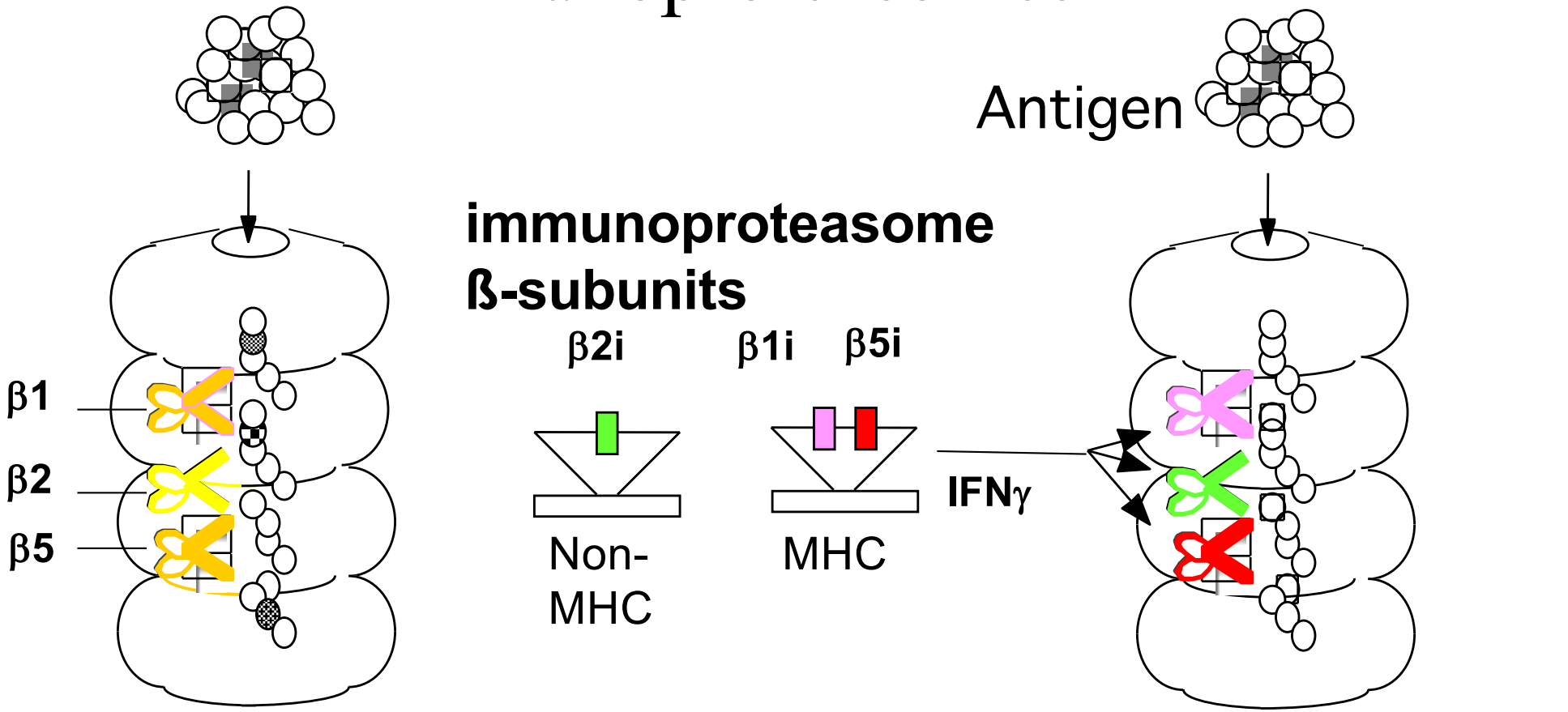
Protein



Active sites

Immune system modification of proteolysis

Immunoproteasomes



Proteasome
(constitutive)

Immunoproteasome

Peptides are 50%
different

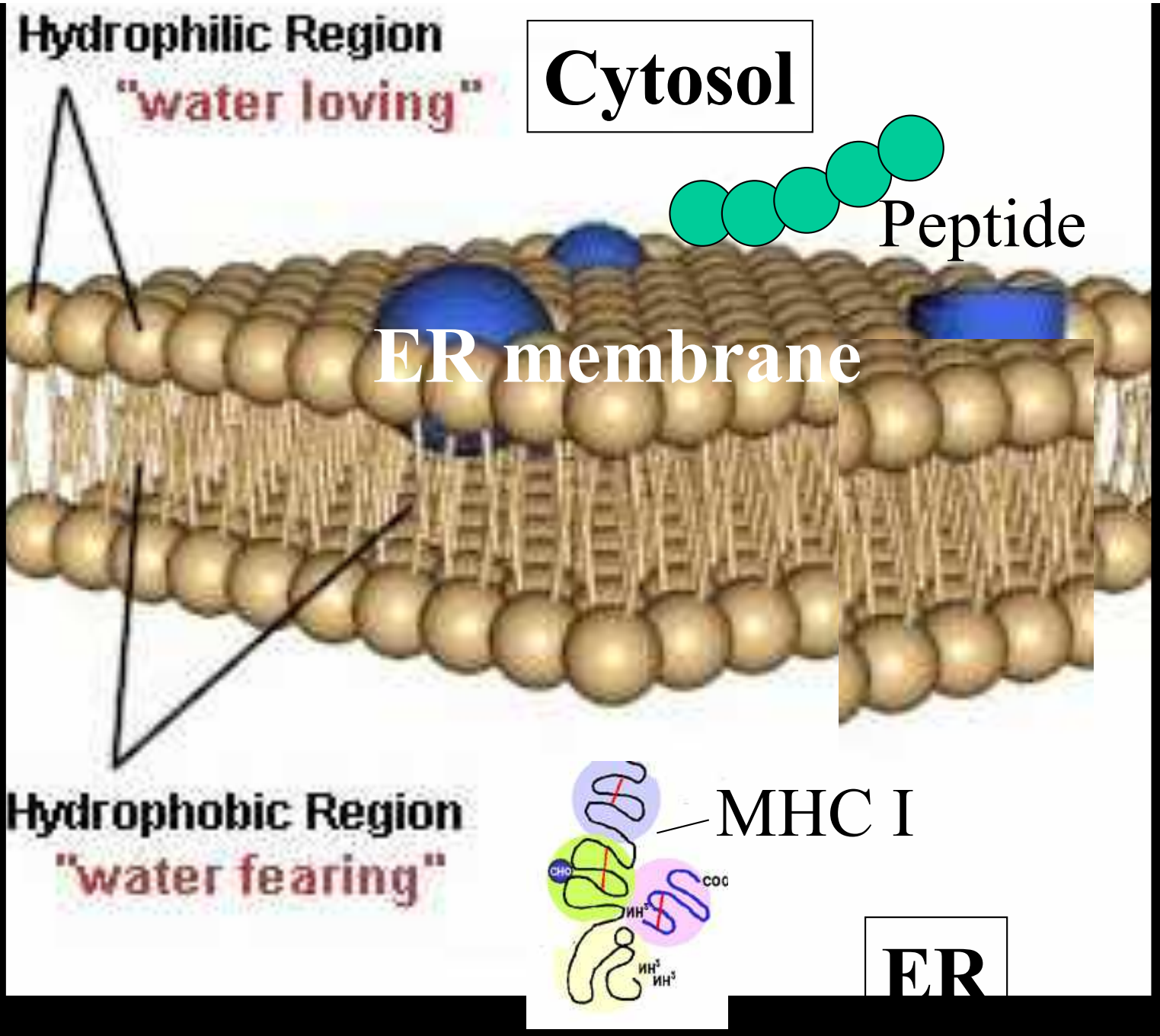
[Also a β5t subunit expressed only in the thymus]

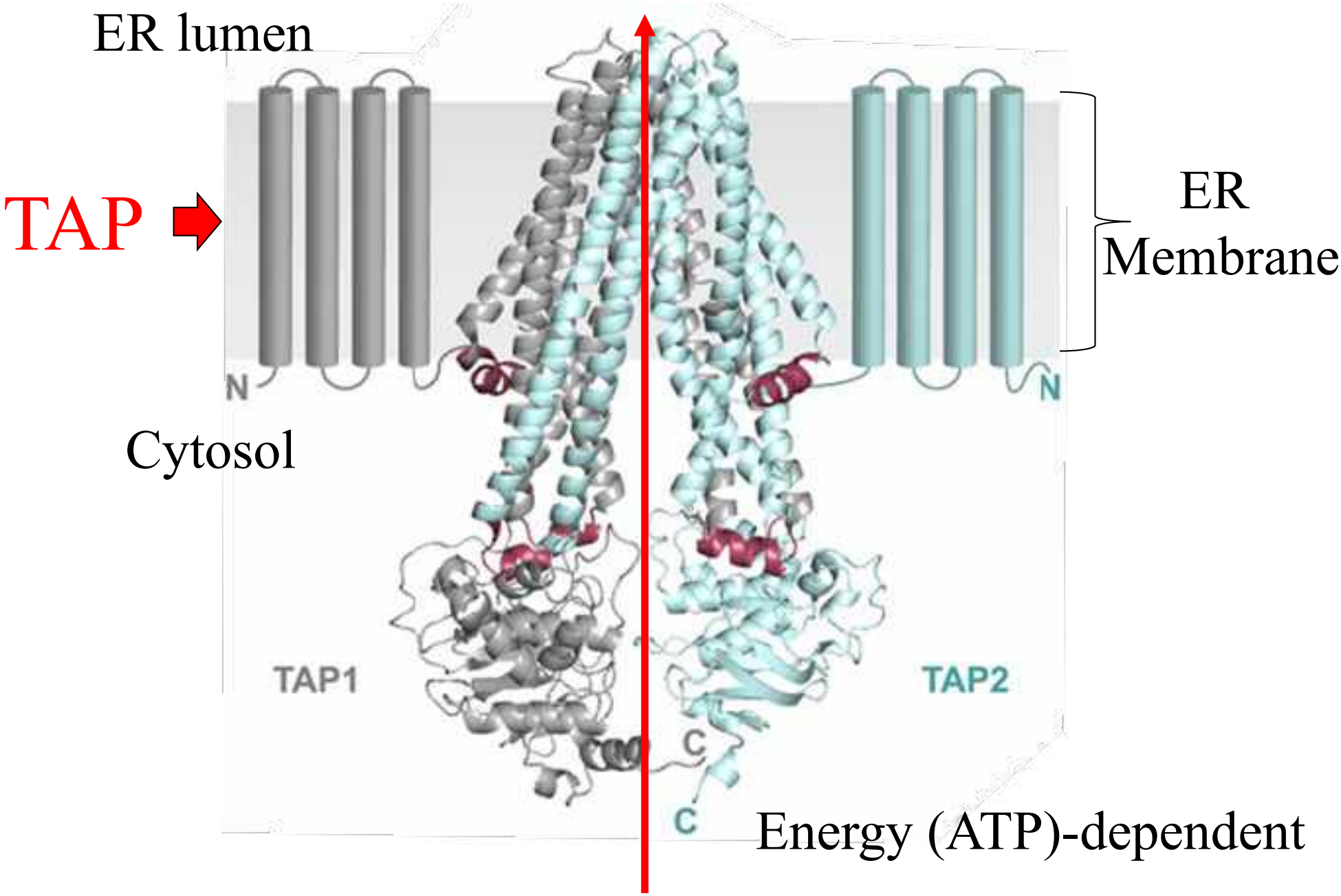
Key points

The proteasome is required to generate the majority of presented peptides

The immune system evolved modifications of proteasomes to optimize antigen presentation.

How do class I molecules access cytosolic peptides?

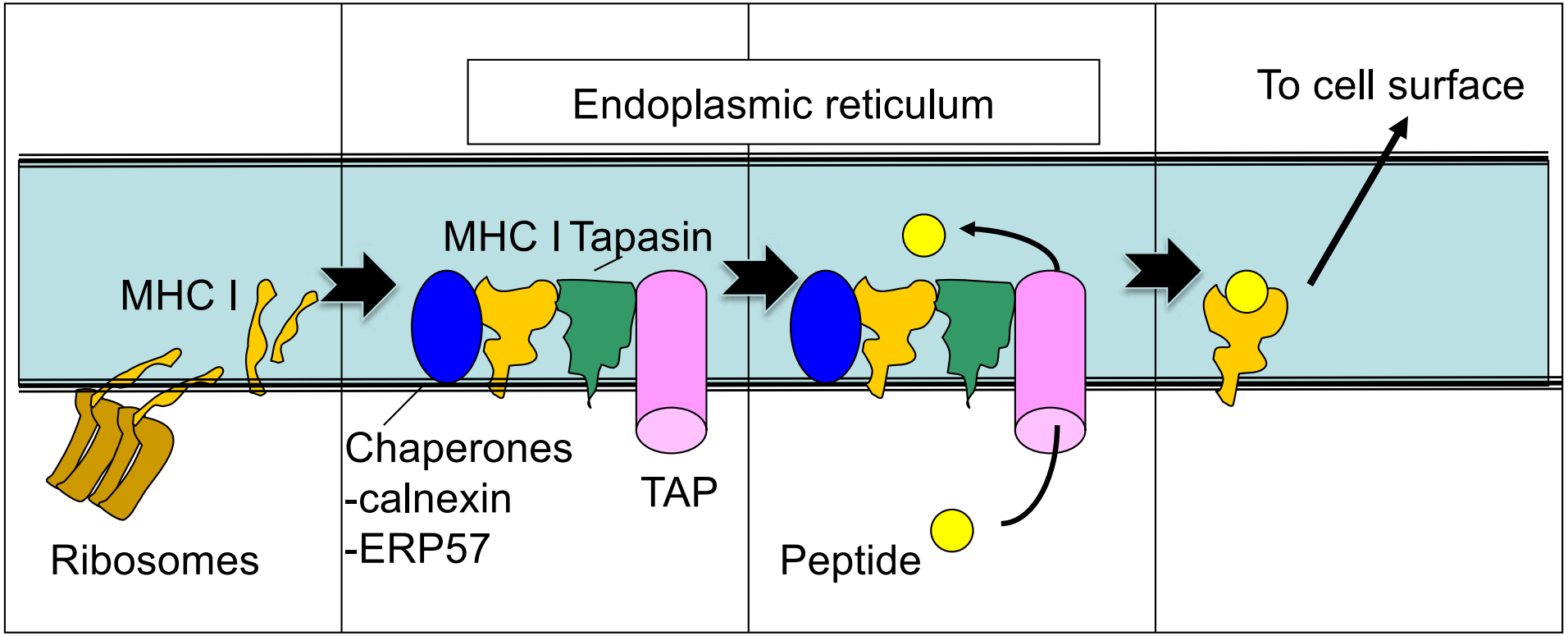




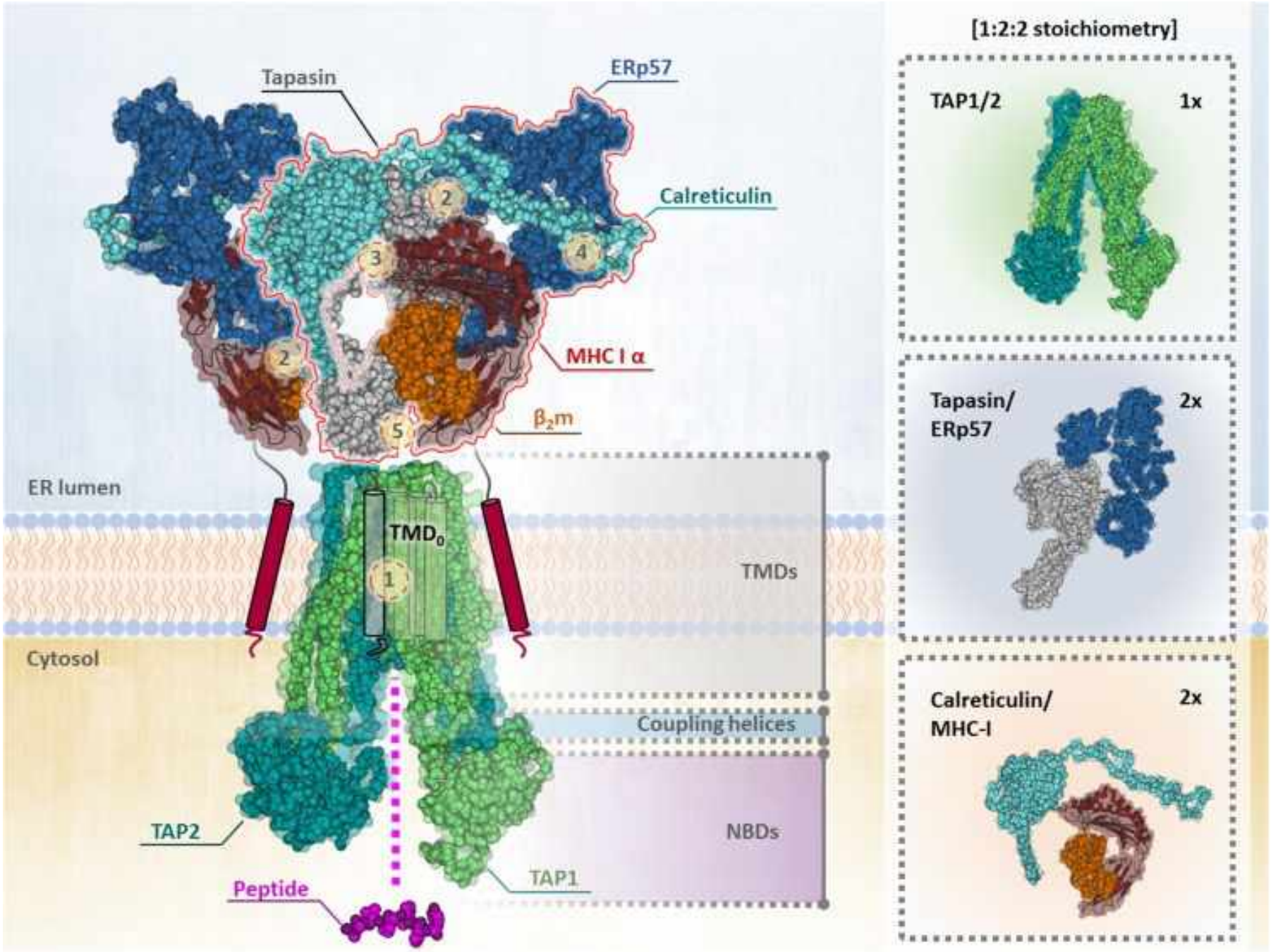
8 to ~16 AA peptides

Most but not all sequences

Other events in the ER



Peptide-loading complex (PLC)

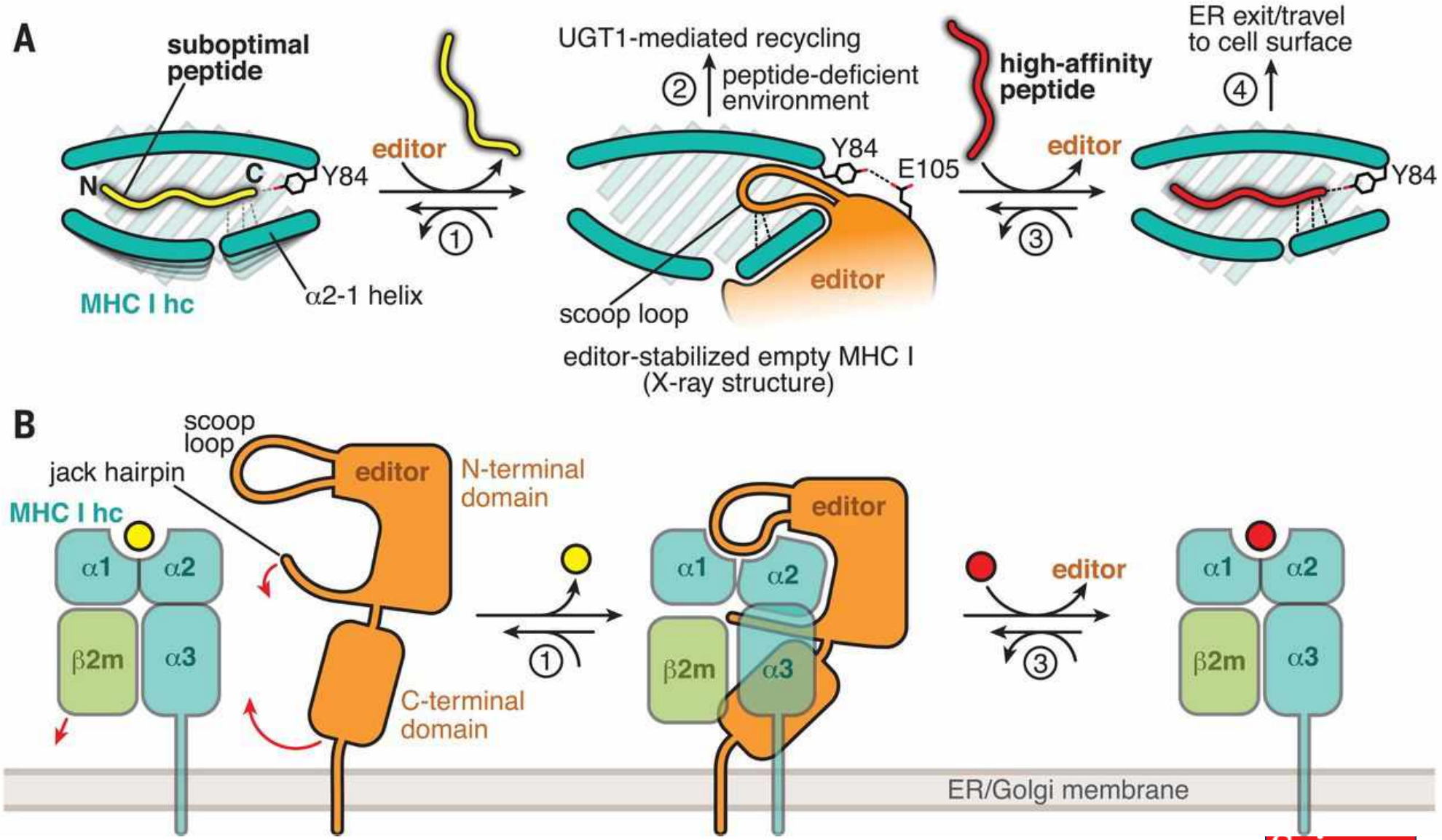


Tapasin (in PLC) & TAPBPR (not in PLC)

Promote & “edit” peptide-loading of MHC I molecules

Tapasin plays a role of retaining “empty” MHC I in the ER

Mechanism of peptide editing



Christoph Thomas, and Robert Tampé Science
2017;358:1060-1064

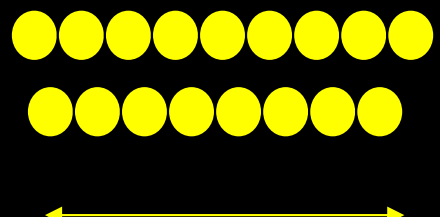
Summary of key points:

- Peptides are generated in the cytosol
- TAP transports a fraction of the cytosolic peptides into the ER
- MHC I molecules form in the ER and associate with TAP and chaperones while awaiting a peptide.
- Peptide editors retain empty MHC I in the ER & help load high affinity peptides

Size of peptides bound by MHC I molecules

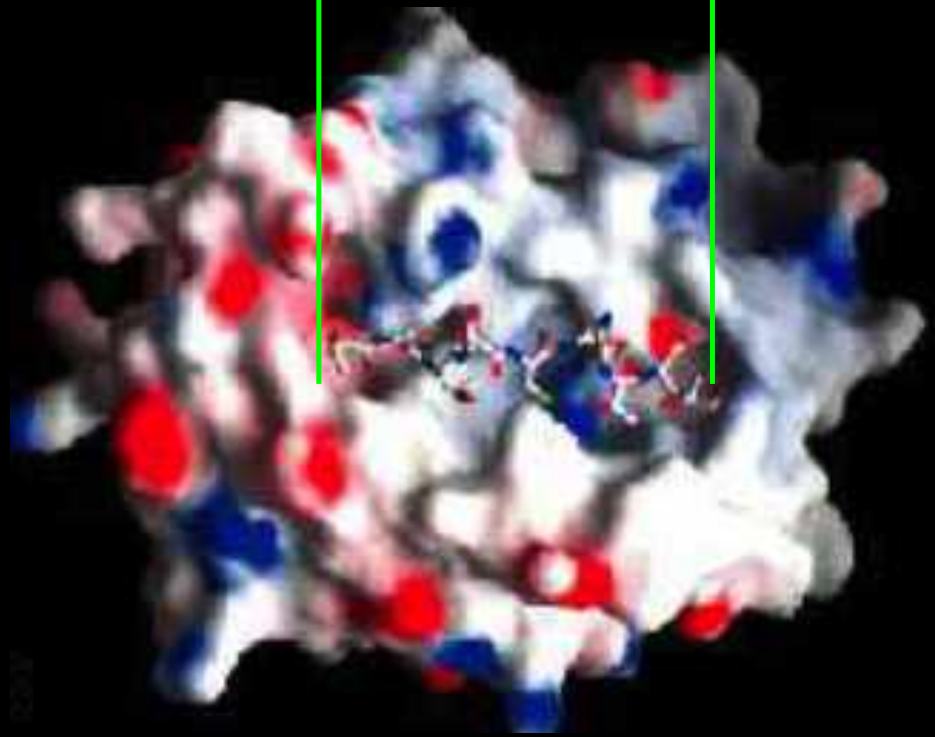
HLA-A,B, C

H2-Kb

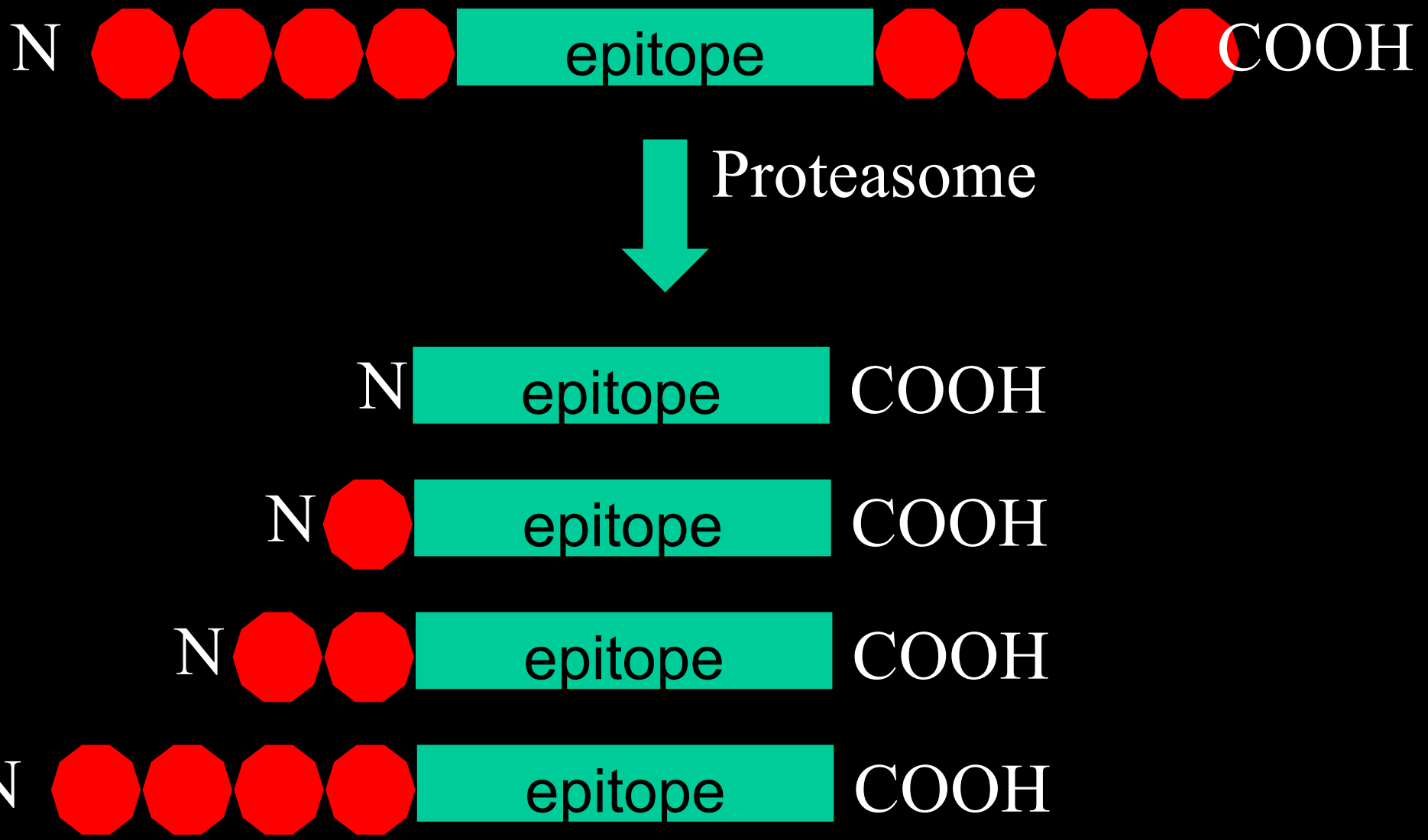


9-10mers

8mers (some 9mers)



Proteasome often make N-extended "precursor" peptides



N-terminal trimming of peptides

Much of the trimming occurs in the ER

By the aminopeptidase = ERAP1/ERAAP

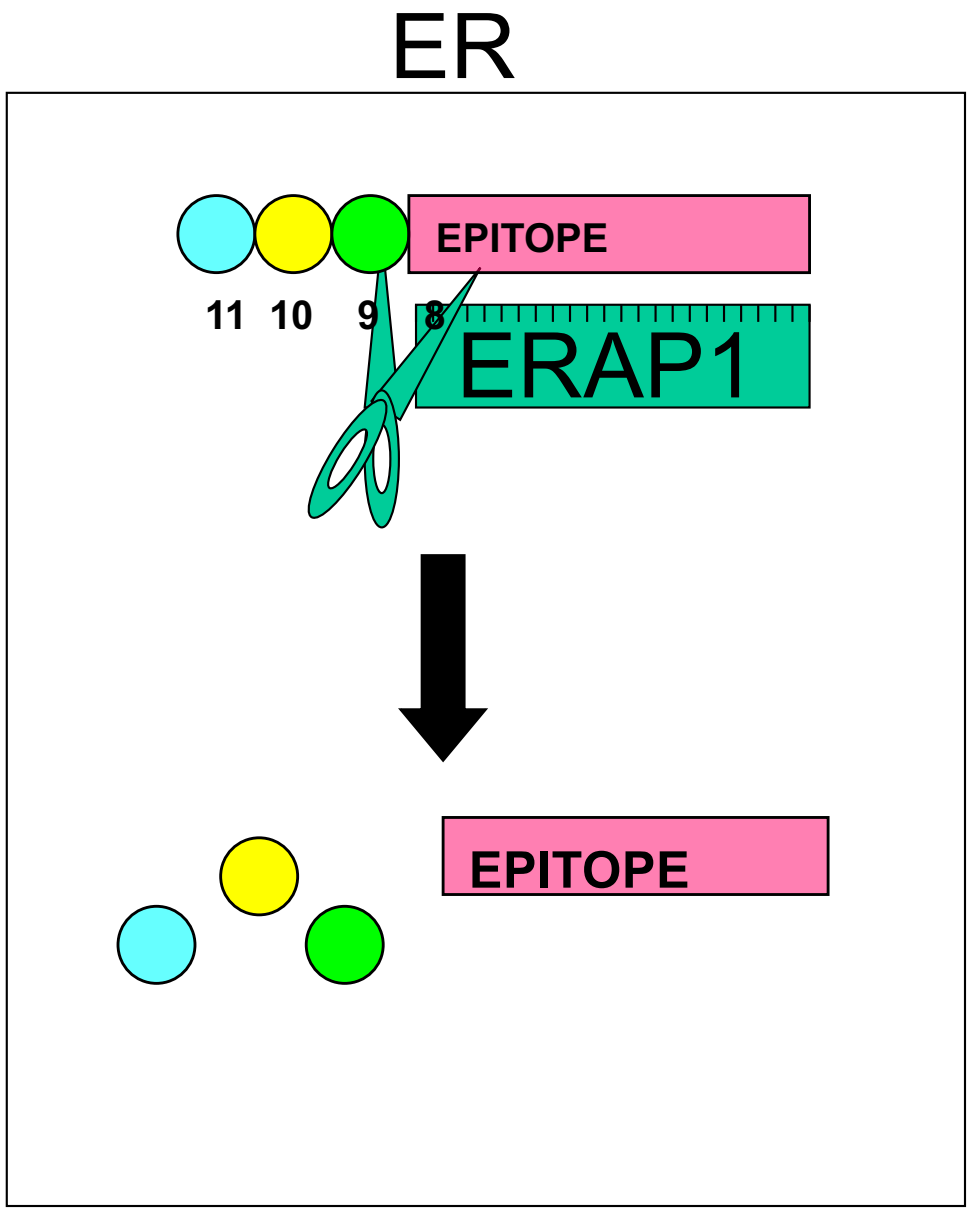
(note humans but not mice also have an ERAP2)

Importance of ERAP1

ERAP1 KO markedly alters MHC I antigen presentation in mice

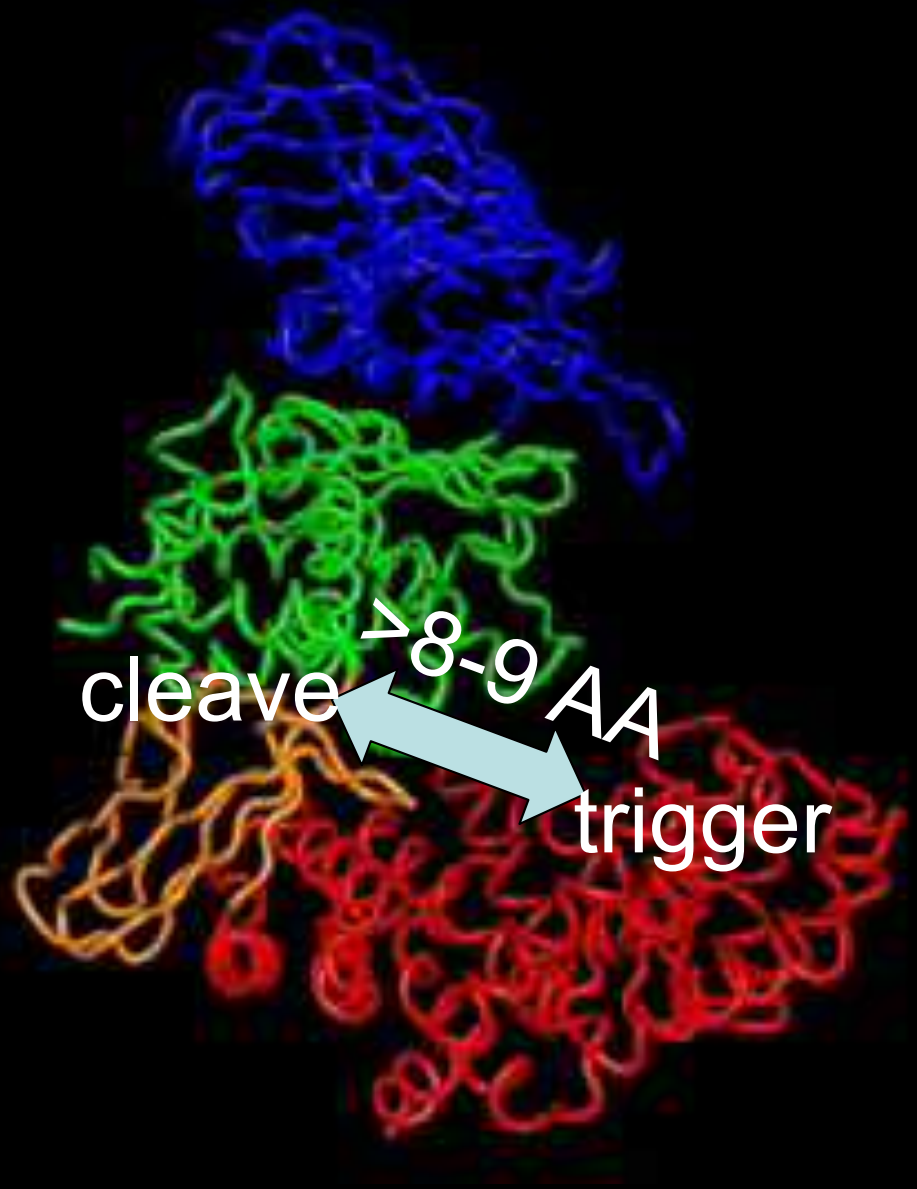
ERAP1 polymorphisms linked to autoimmune diseases and immune responses.

ERAP1 unique-trims with a molecular ruler



Nature Immunology, 3: 1169-1176

Crystal structure



Cytosol trim

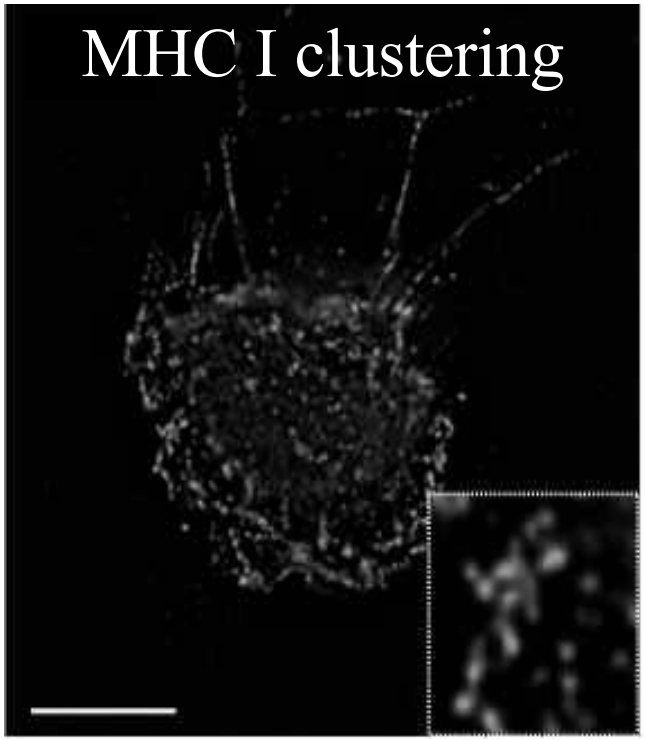
Summary

N-extended peptides are trimmed in the ER by ERAP1

ERAP1 trims with a molecular ruler

ER Trimming has specificity

Influences responses



Plasma Membrane

TSPAN5

TSPAN5 membrane domain

MHC I in PLC

ER

MHC
Heavy
chain

ß2M

Ribosomes

Empty
MHC I

Calreticulin

ERP57

Tapasin

TAP

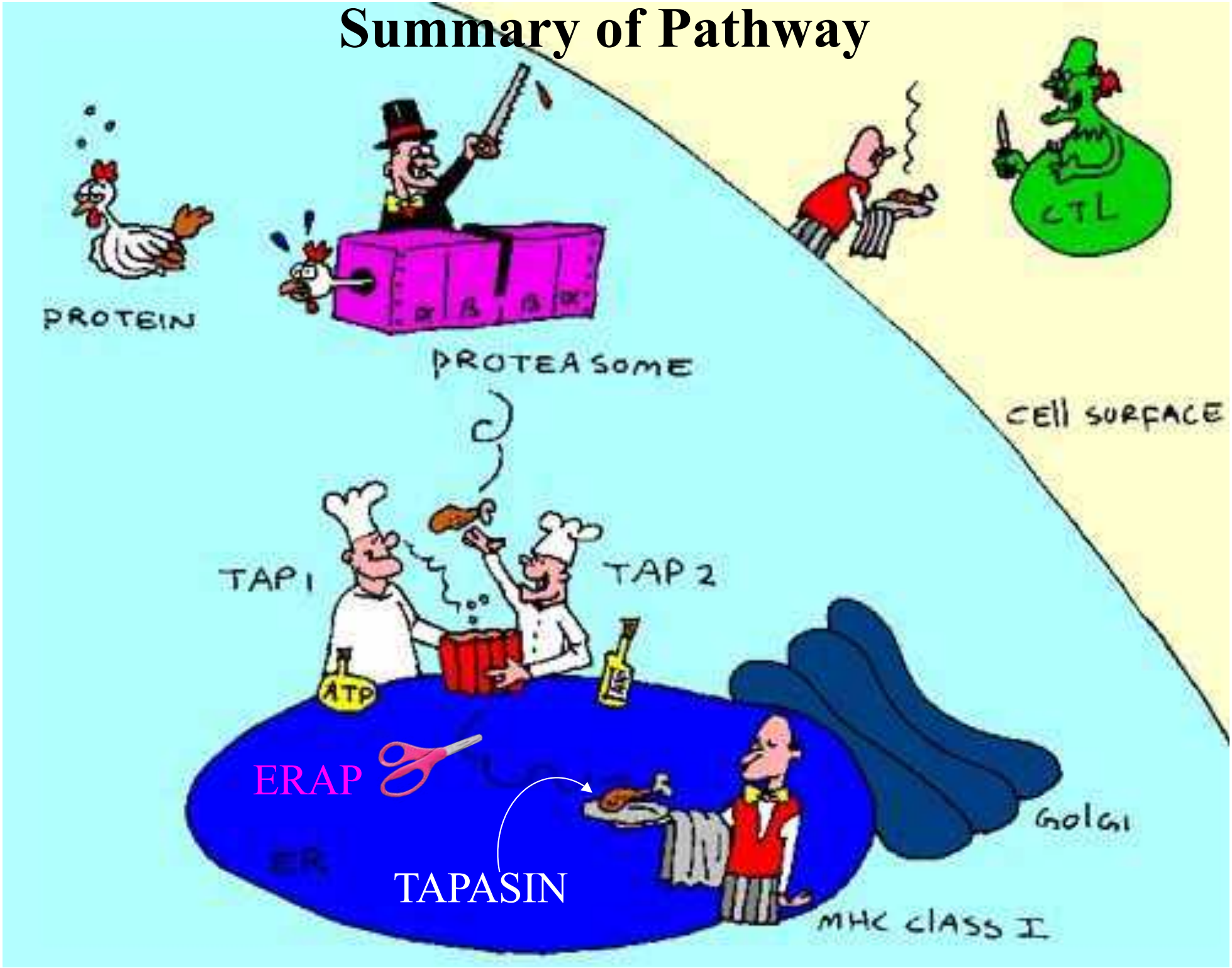
Peptides

pMHC I

TSPAN5

TSPAN5 Mb domain

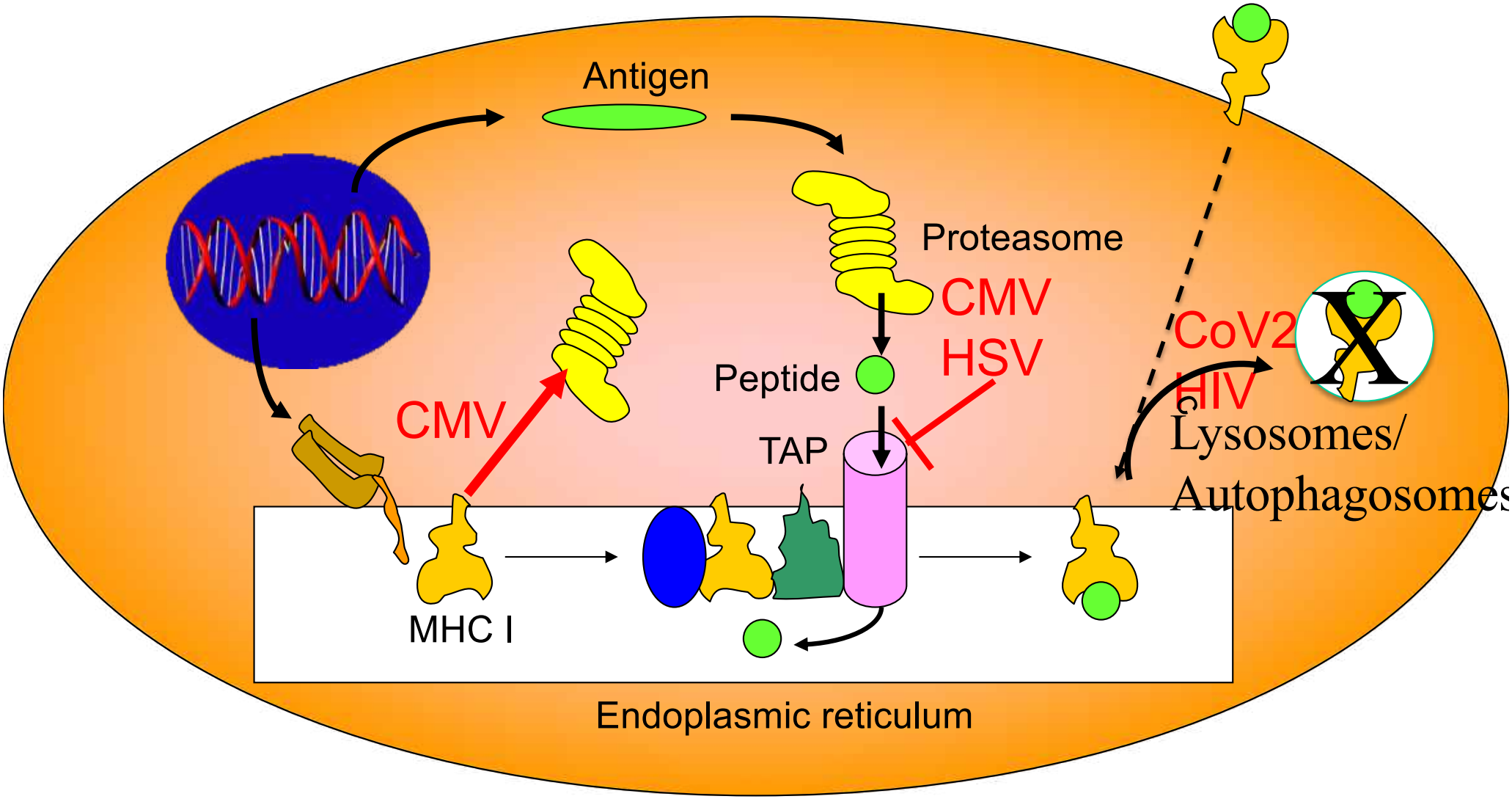
Summary of Pathway



Antigen presentation is a “bell & whistle”

MHC I molecules, tapasin, TAP transporter, immunoproteasomes, ERAP1 are not required for cell viability

Viral Immune evasion



Cancer immune evasion

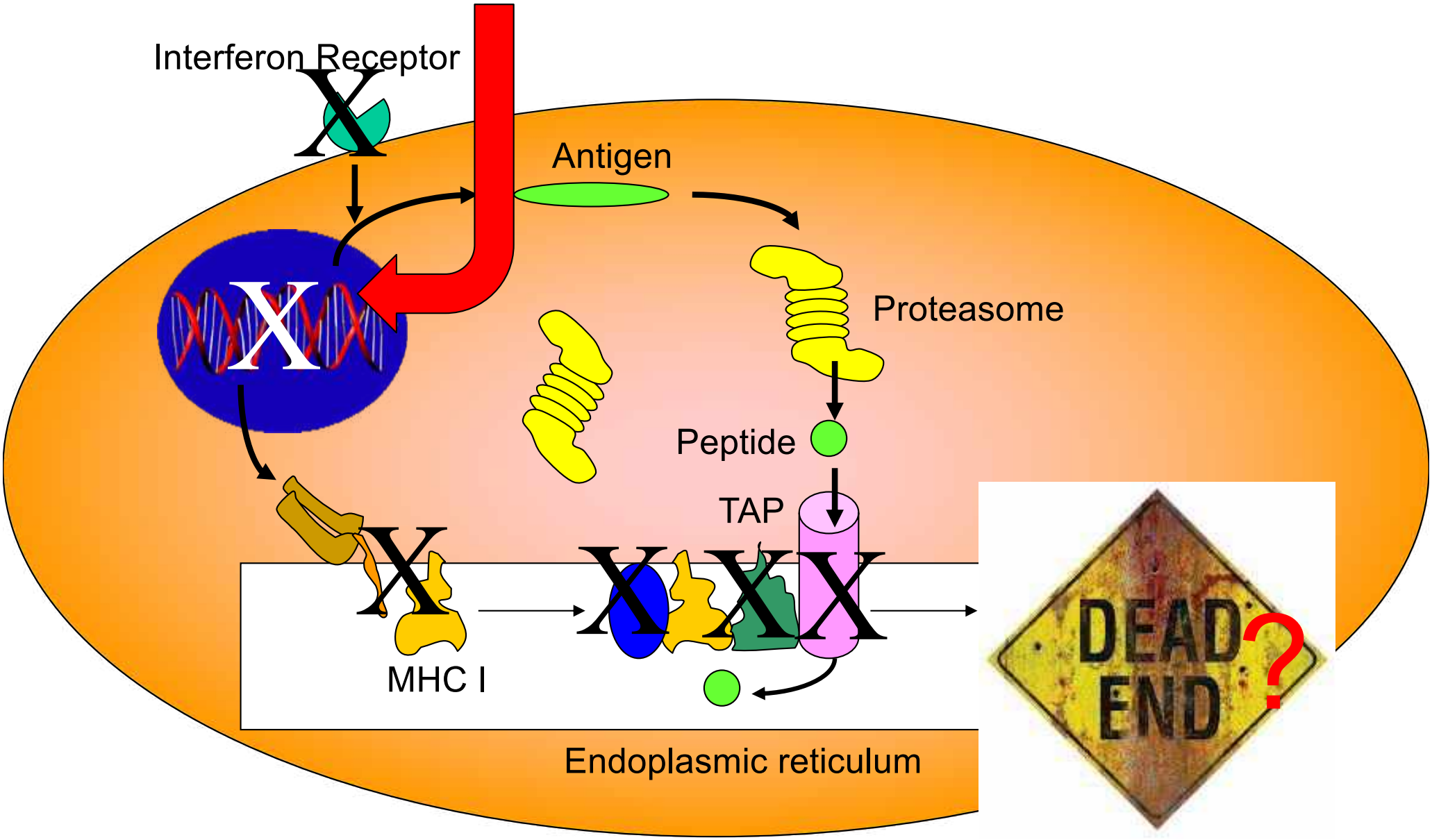
To survive & progress, cancers need to evade CD8 T cells

Evasion by loss of the MHC I pathway is very frequent

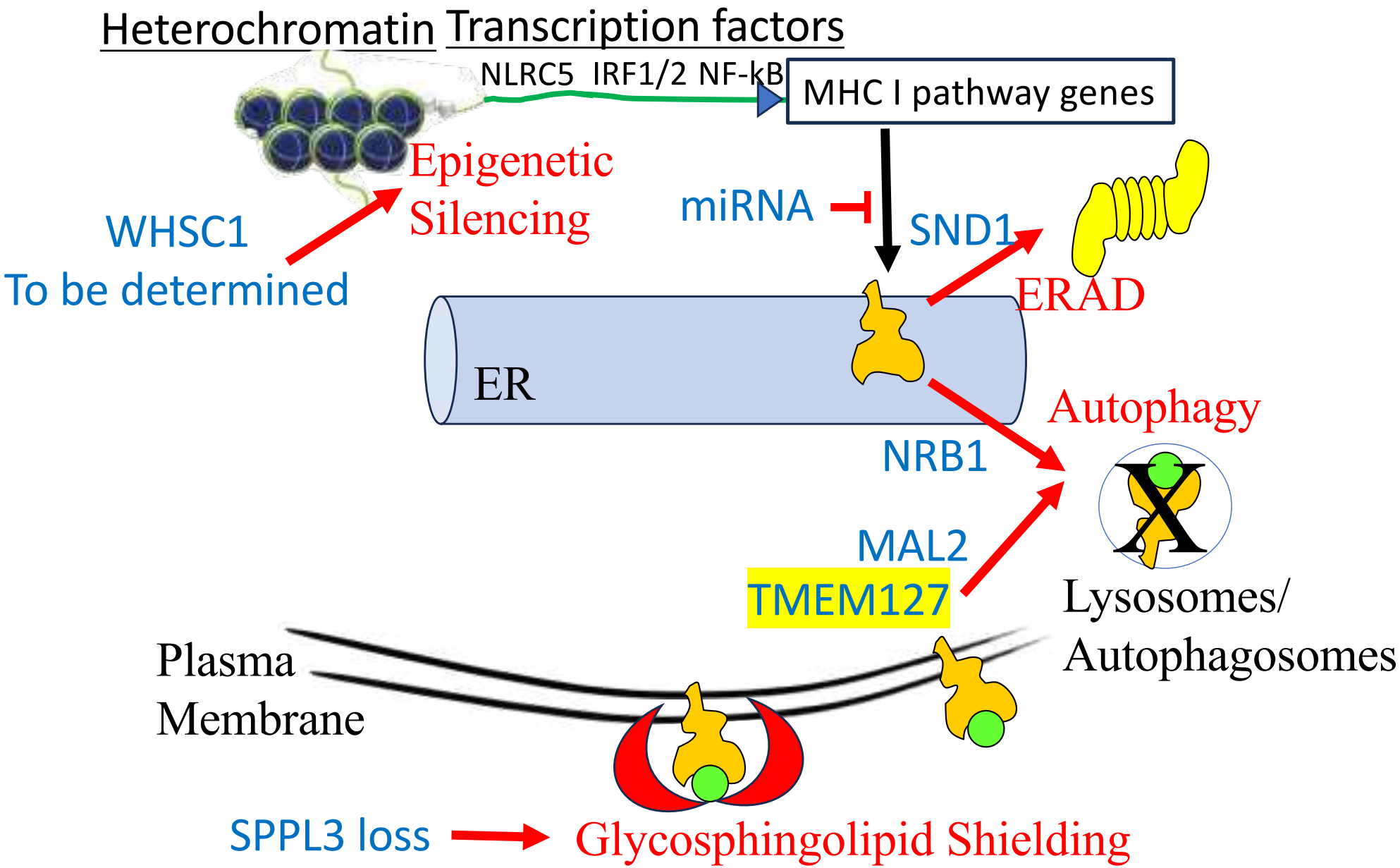
This is a barrier to T cell-based cancer immunotherapy

Cancer immune evasion

Loss of key MHC I pathway genes

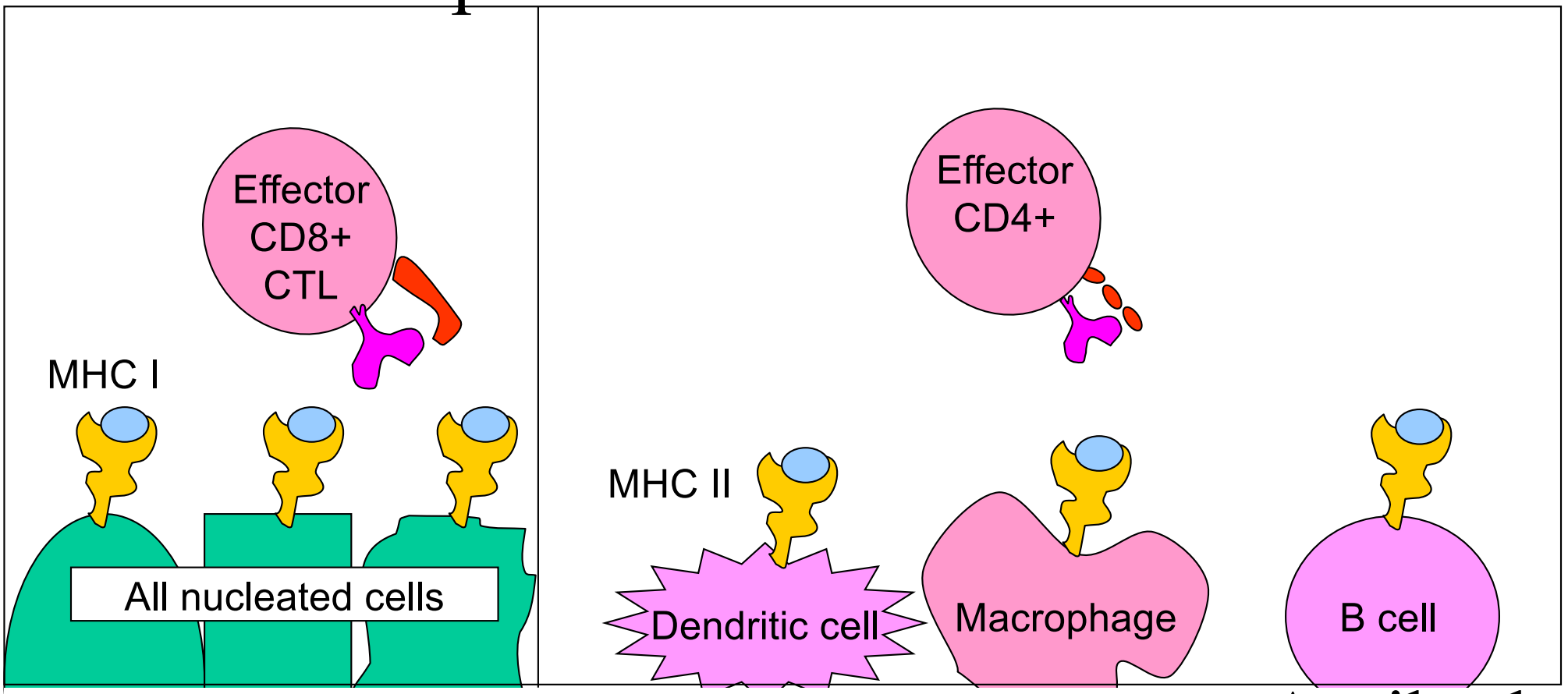


Transcriptional & post-transcriptional evasion



MHC II antigen presentation

What cells express MHC class I & II molecules?



Target Killing

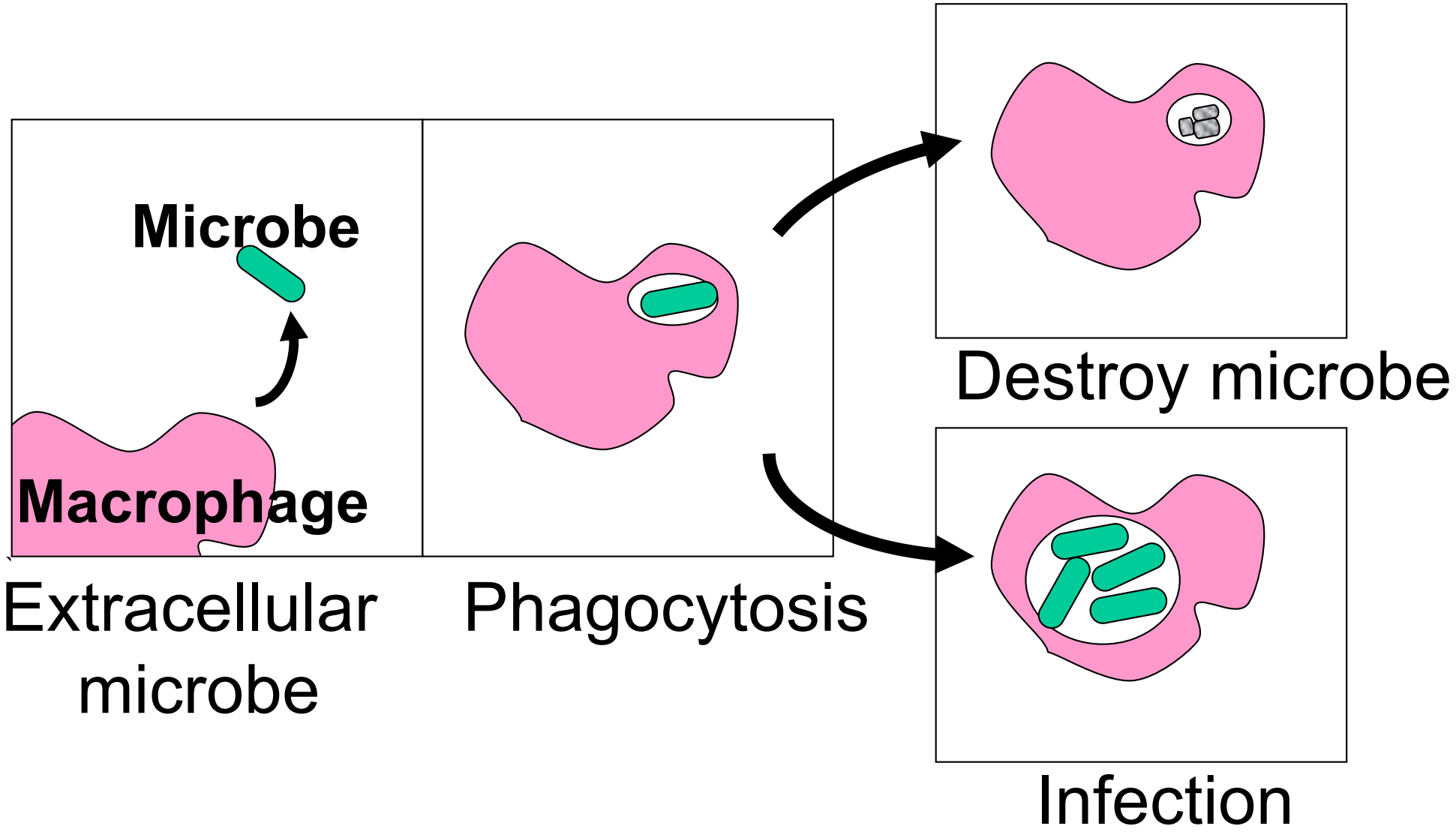
T cell priming

MØ activation

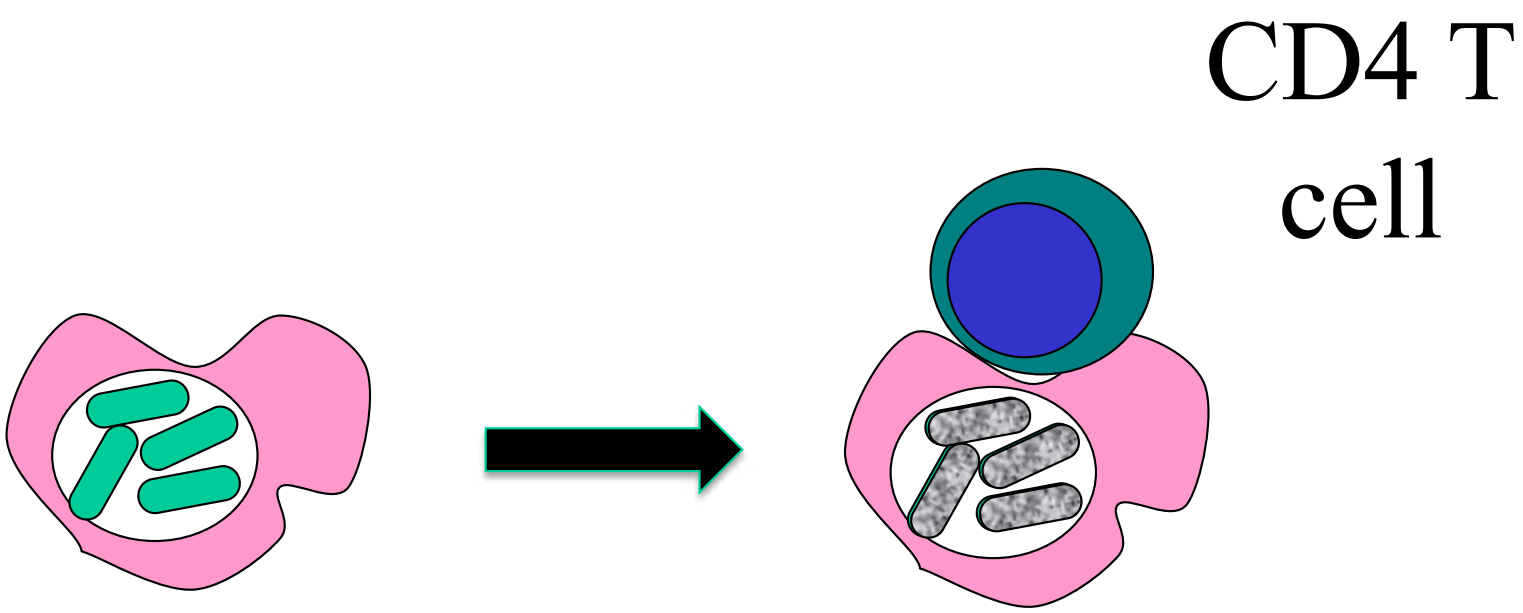
Antibody responses

These are precisely the cells that T cells need to monitor

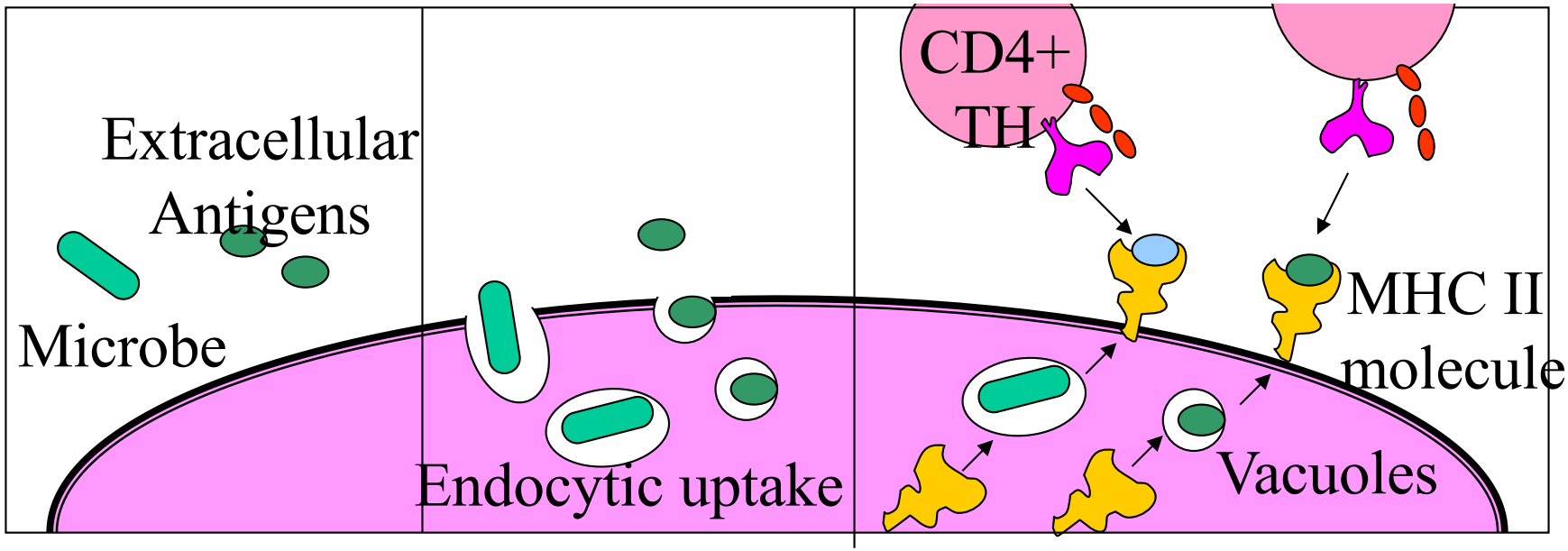
Outcomes of bacterial infection



The major immune defense against cells infected with bacteria are CD4 T cells



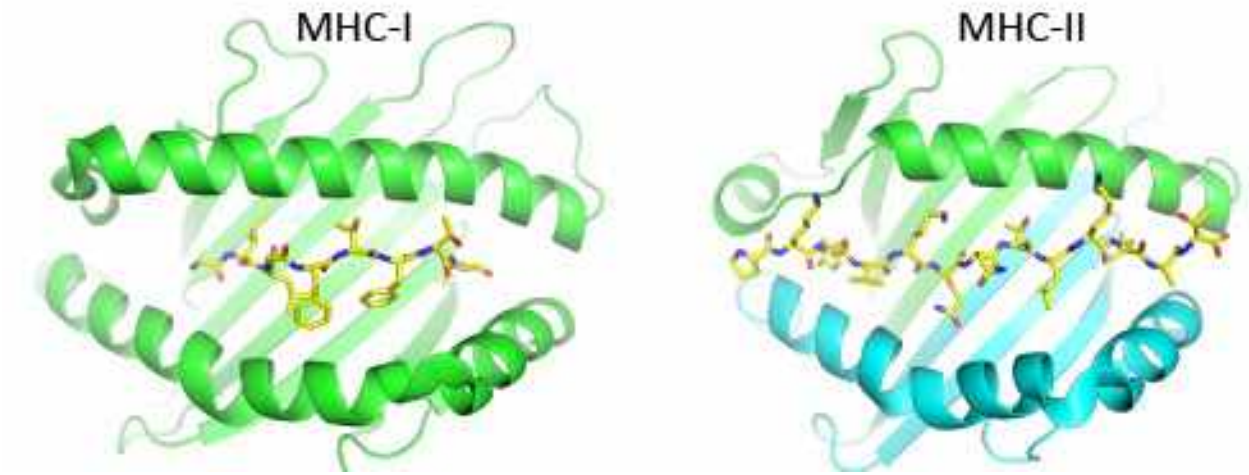
MHC II sample peptides in endocytic compartments



MHC II peptide-binding receptors

3 molecules = HLA-DR, DP, DQ

Very similar tertiary structure to MHC I

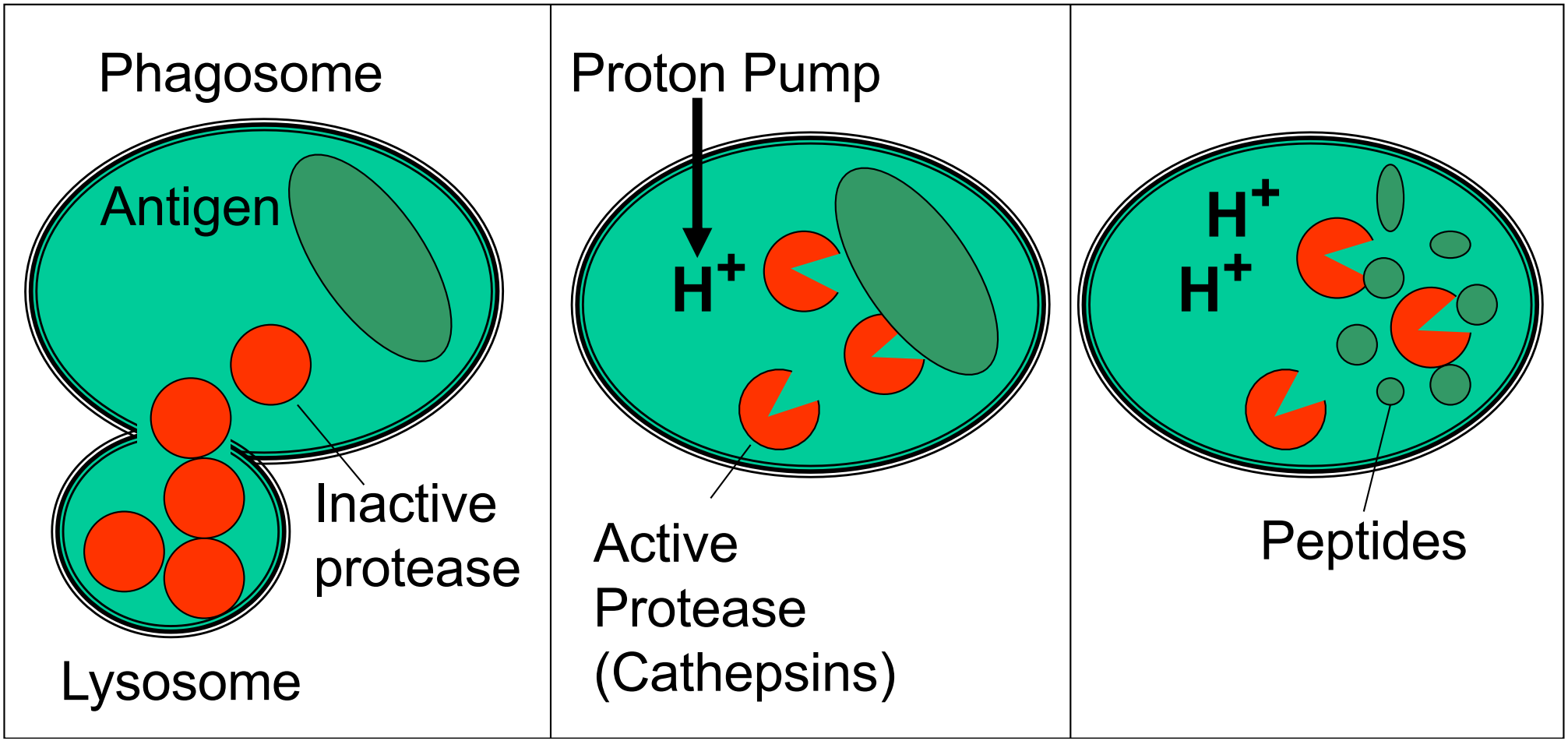


Same regions highly polymorphic

MHC II monitors peptides from phagosomes (& endocytic compartments)

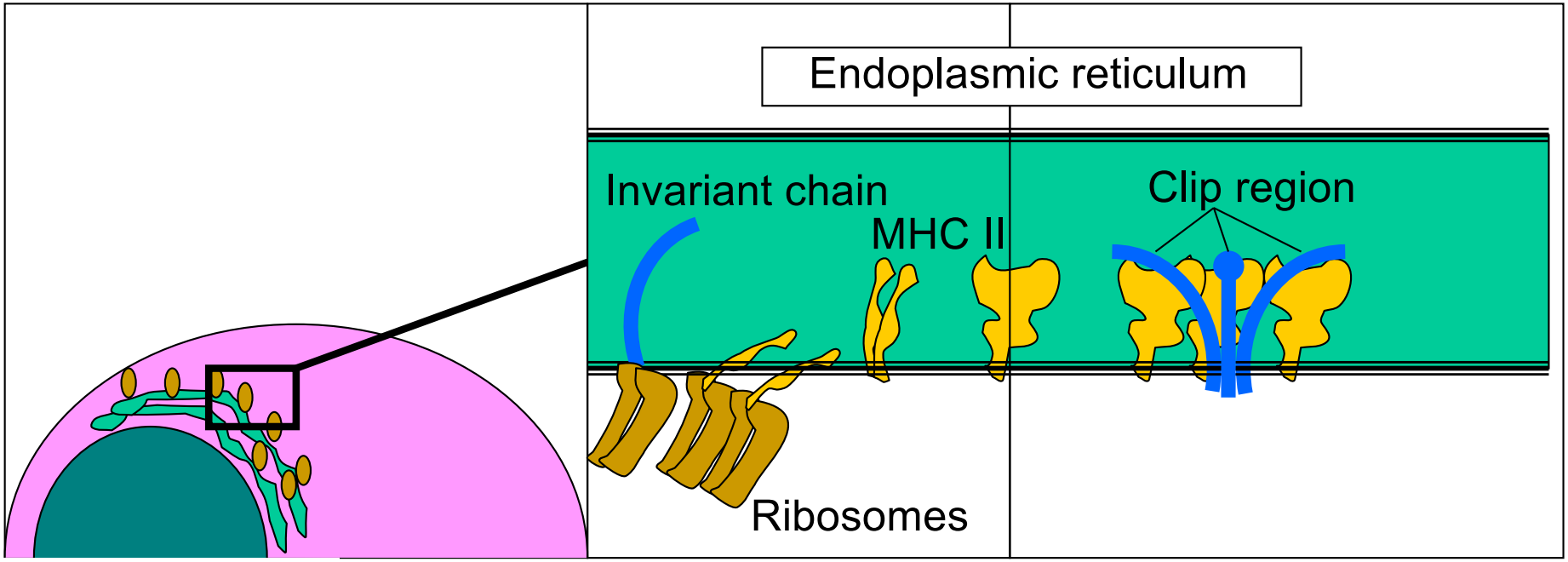
How are these generated?

The endocytic compartment is also catabolic.



How do class II molecules get to phagosomes/endosomes to sample these compartments

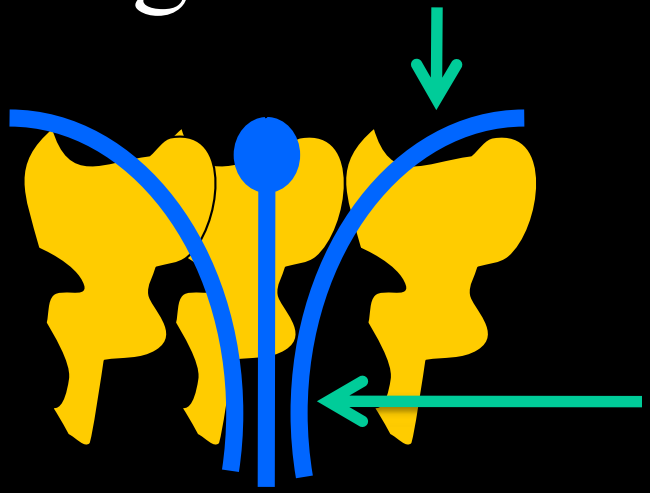
Synthesis & assembly of MHC class II molecules



How is class II prevented from being saturated with peptides in the ER & then get to the right compartments?

Invariant chain

Clip region blocks the groove

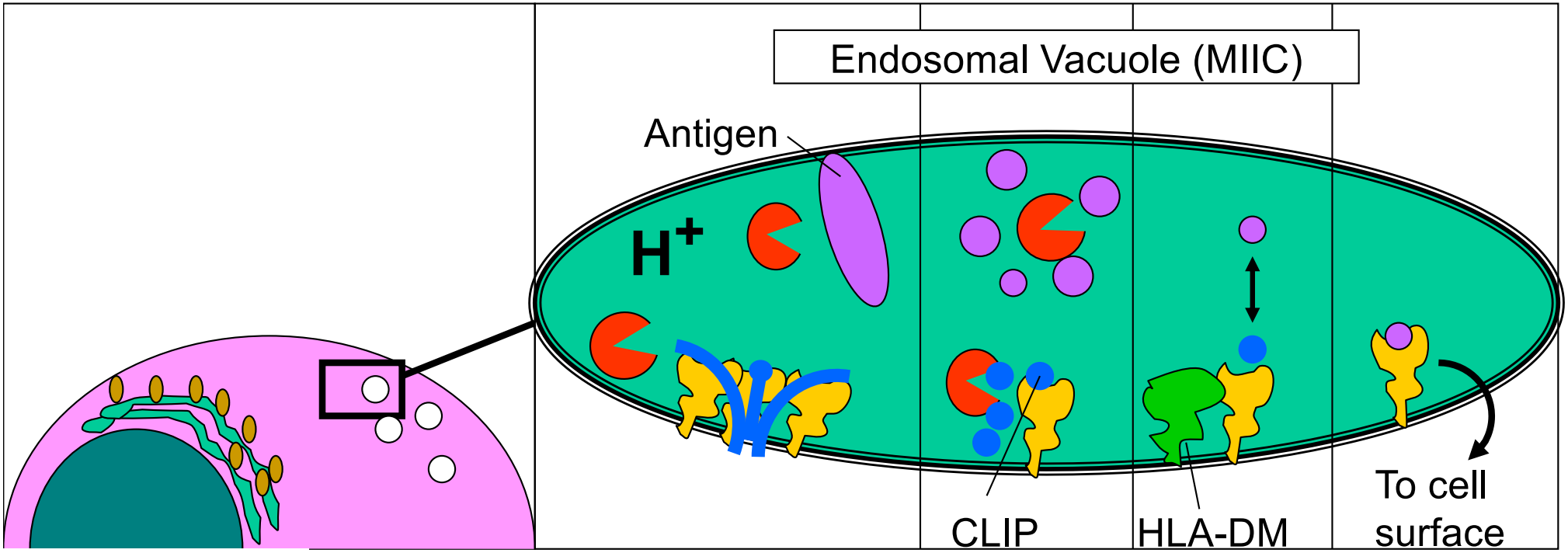


Sorting sequence to endosomes

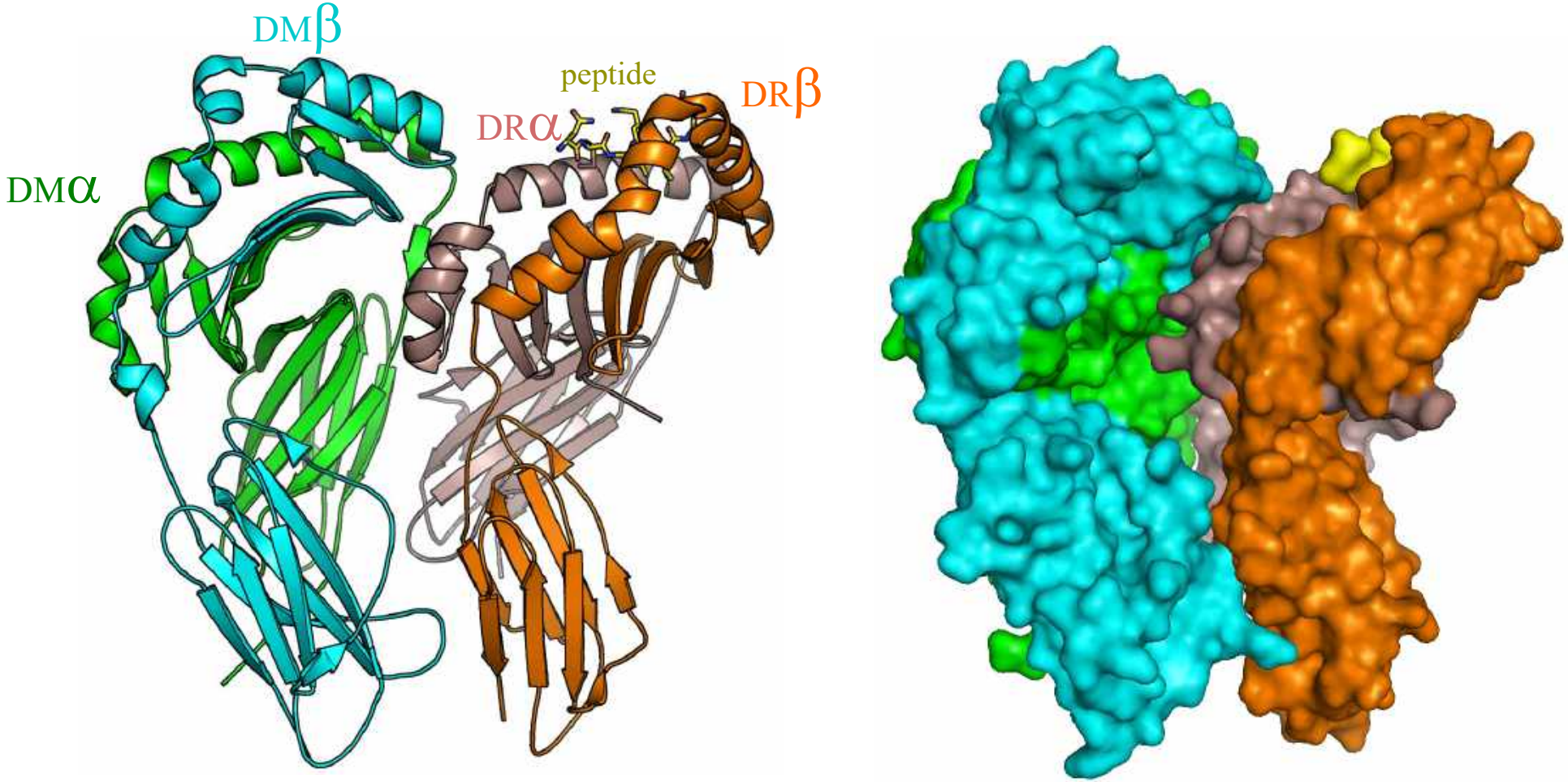
Key points

- Invariant chain binds newly synthesized class II in the ER
- Invariant chain blocks peptide binding to class II
- Invariant chain directs class II molecules to endocytic compartments
- Peptides are generated in endosomal compartments by acid optimal proteases

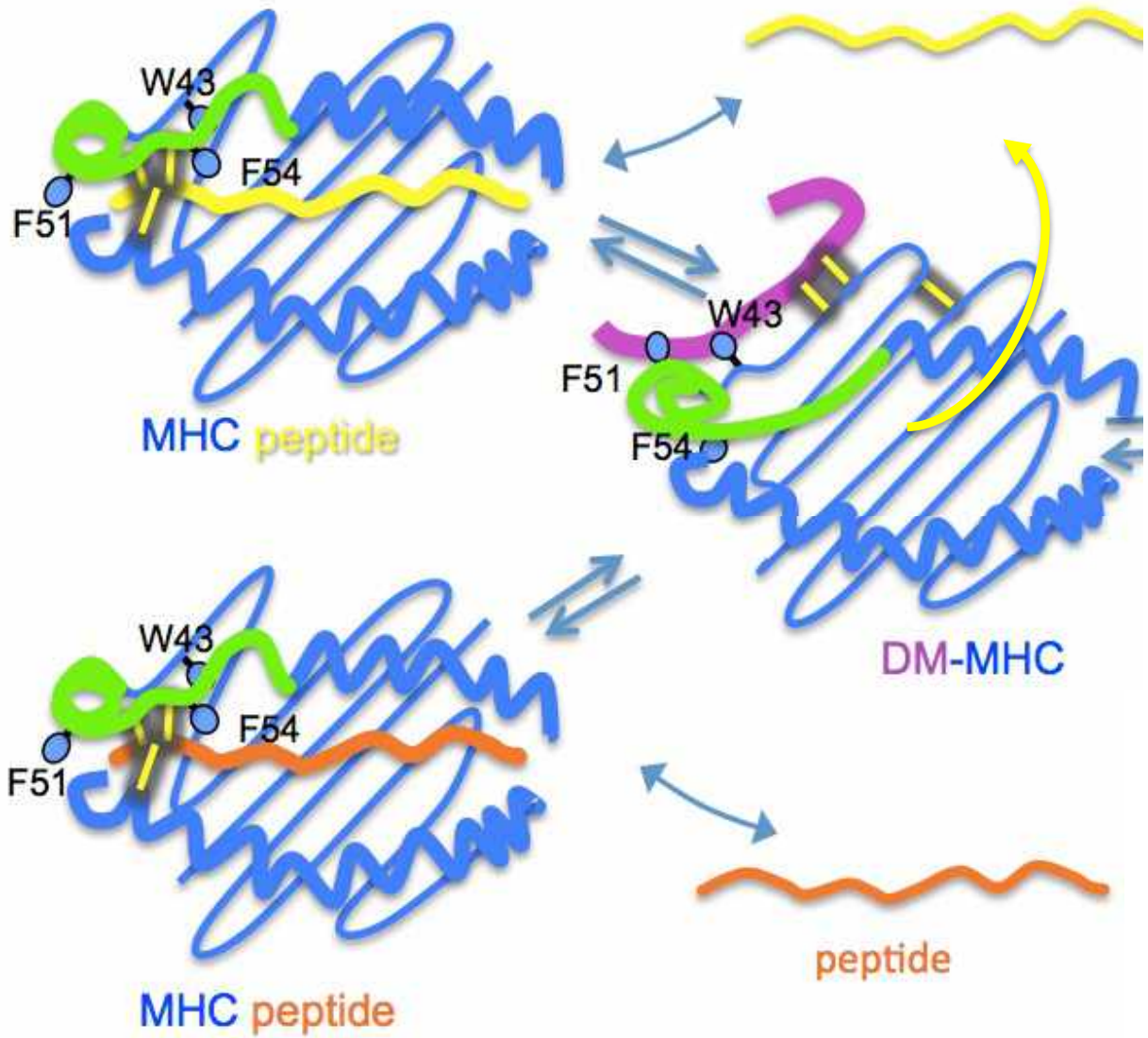
How are class II molecules activated in endosomal vesicles?



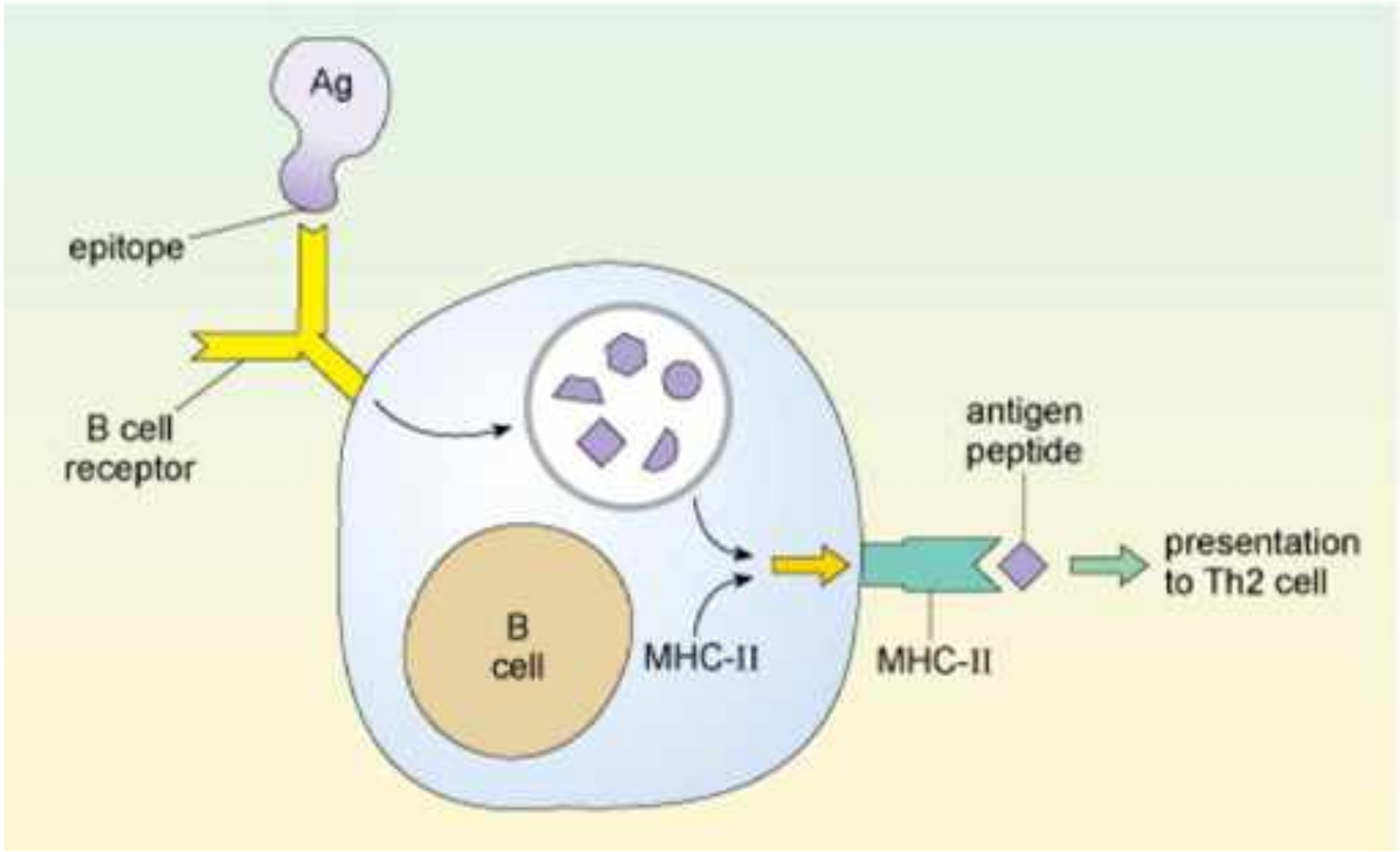
DM-MHCII interaction
(from crystal structure of a trapped complex)



Model for DM-dependent peptide exchange



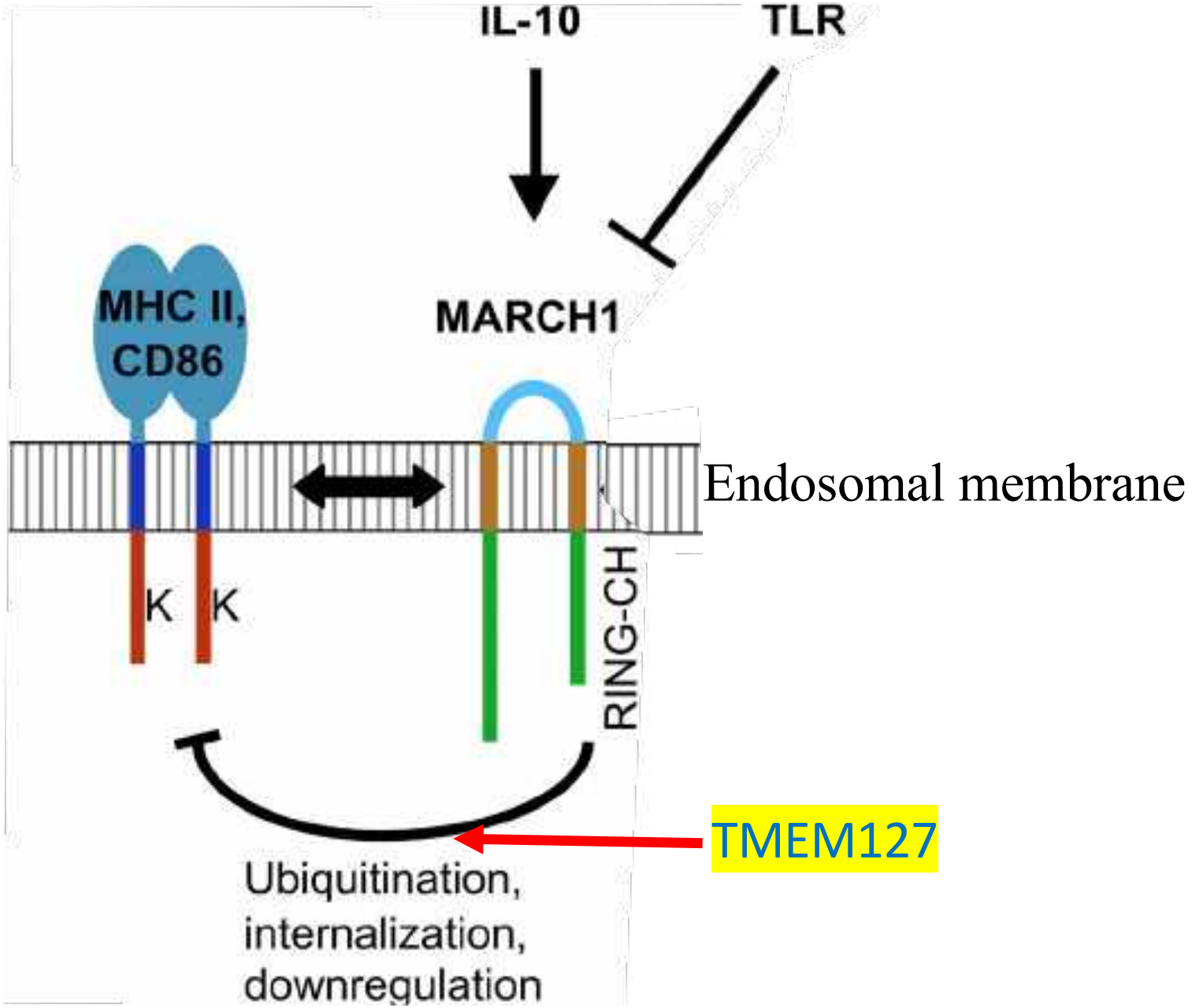
Specialization: B cell antigen presentation



B cells efficiently capture Ag through their surface antibody & internalize it into the MHC II pathway.

Important for T-B cell help

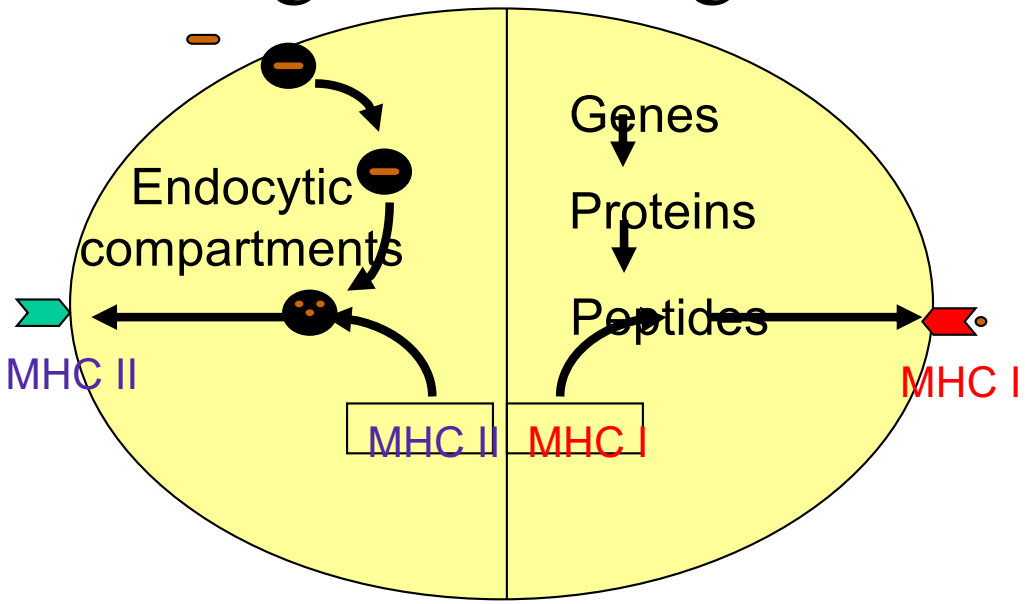
Regulation of MHC II (one aspect)



Key Points

- Invariant chain is hydrolyzed by proteases in the endocytic compartment
- A fragment of invariant chain (CLIP) is left in the peptide binding groove
- CLIP is removed by HLA-DM
- Peptides bind to class II molecules (facilitated by HLA-DM)
- MHC II levels regulated by March I

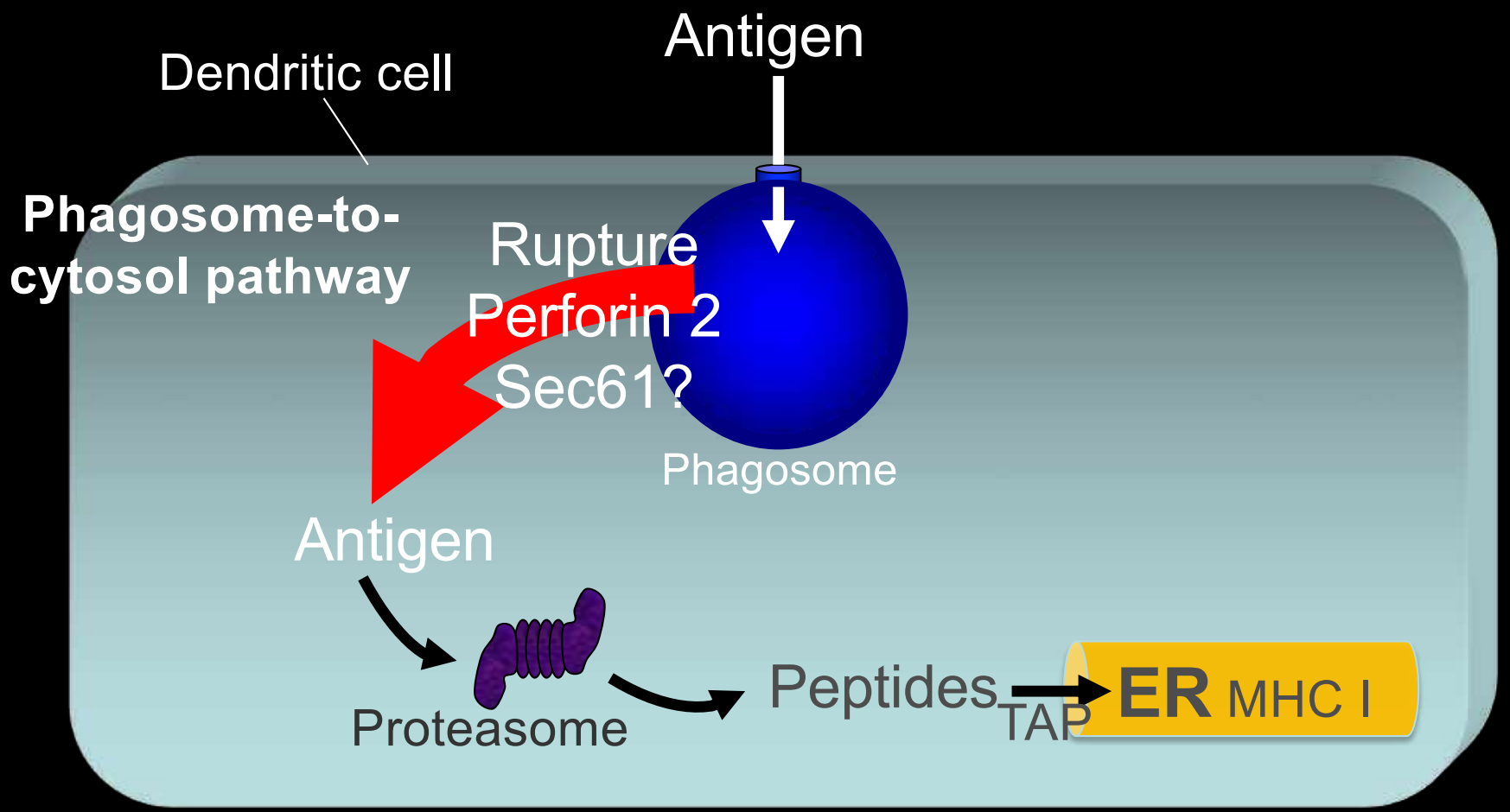
So far we've discussed: MHC I presents endogenous antigens & MHC II presents exogenous antigens



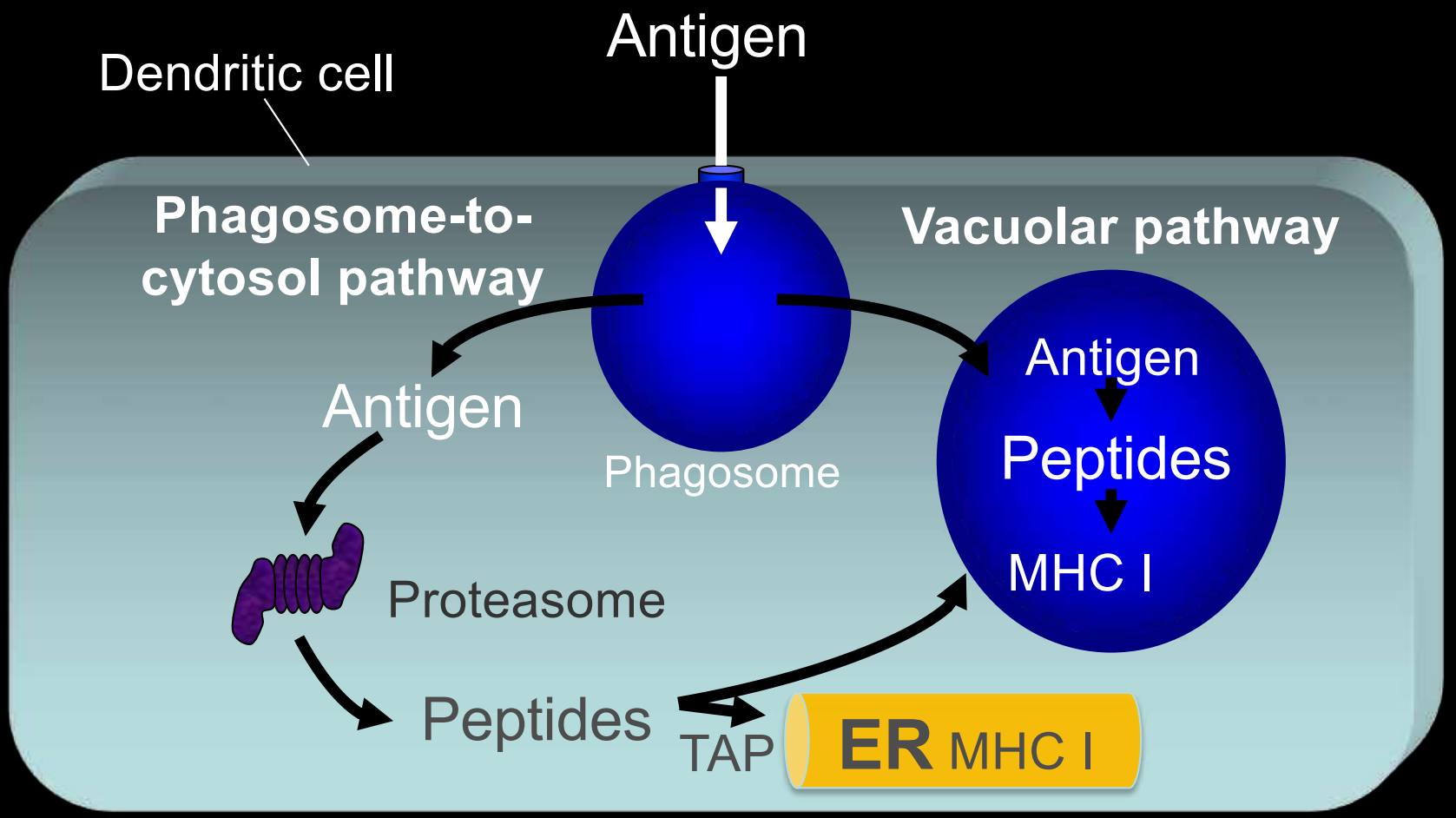
Cross presentation = presentation of exogenous antigens on MHC I

Property of Dendritic cells & MØs

DCs can transfer eaten antigens into the MHC I pathway (called cross presentation)

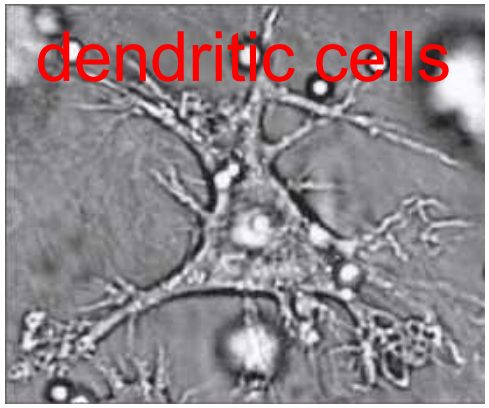


DCs can transfer eaten antigens into the MHC I pathway (called cross presentation)

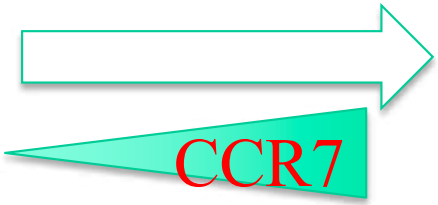


Dendritic Cells- Key APC for initiating T cell responses (priming)

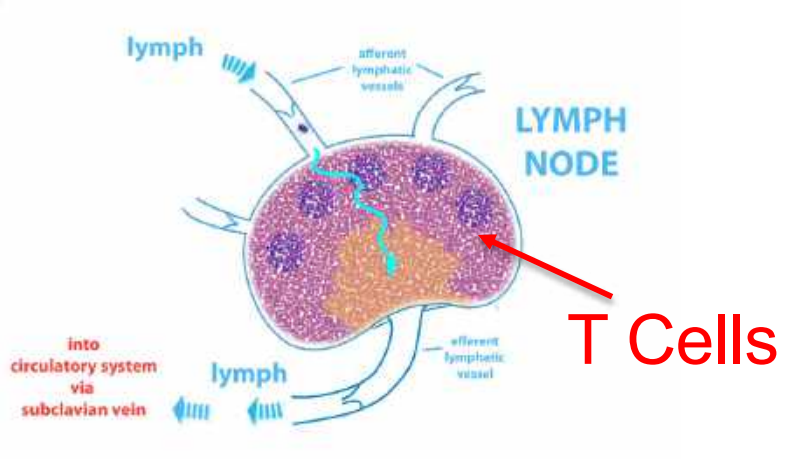
TISSUES



LYMPHATICS



LYMPH NODE



Territory scouts

Trails

Fort Soldiers