Cellular immunity and cancer

Prof. dr. Jannie Borst, head Division of Tumor Biology & Immunology NKI-AVL

Cancer cells and immune cells communicate:
A reflection of the normal response to infection and cellular damage

Tumor cells

Macrophages

Granulocytes

Dendritic cells

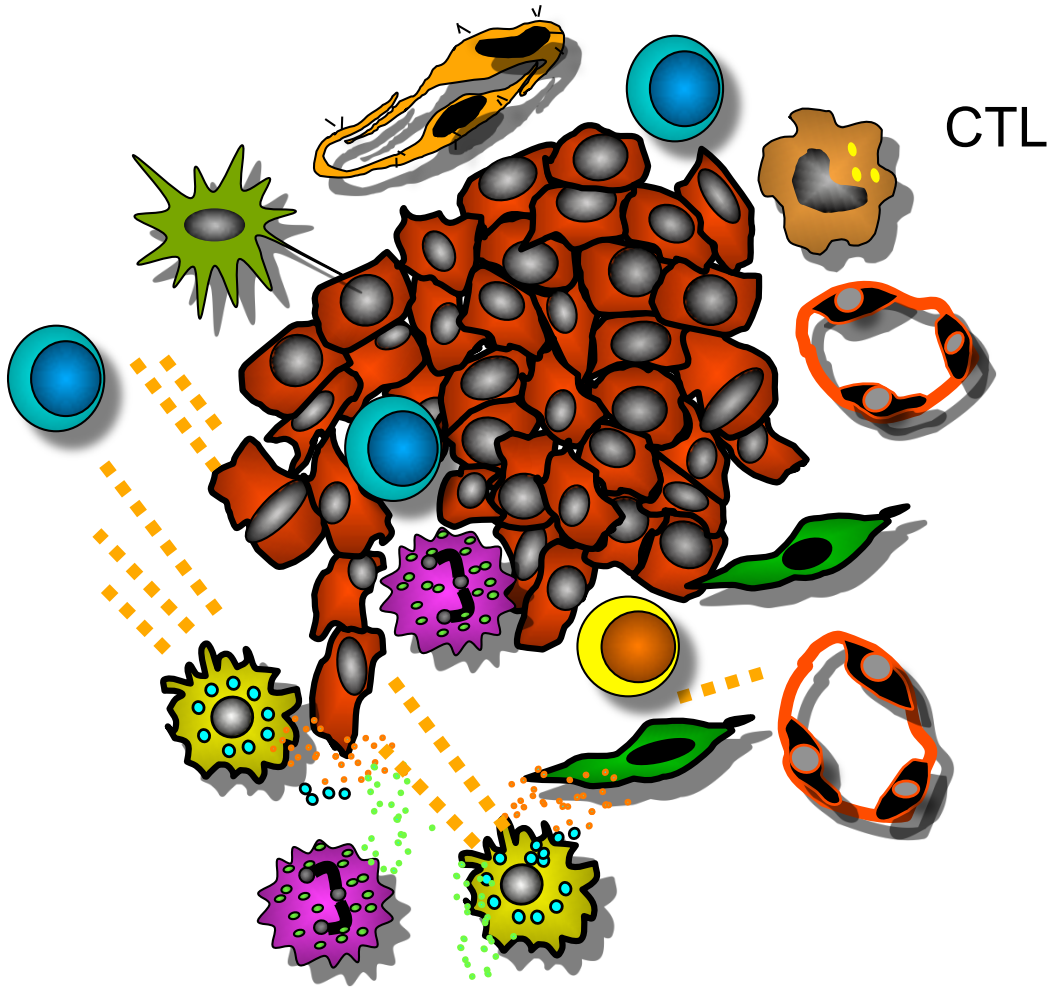
NK(T) cells

B cells

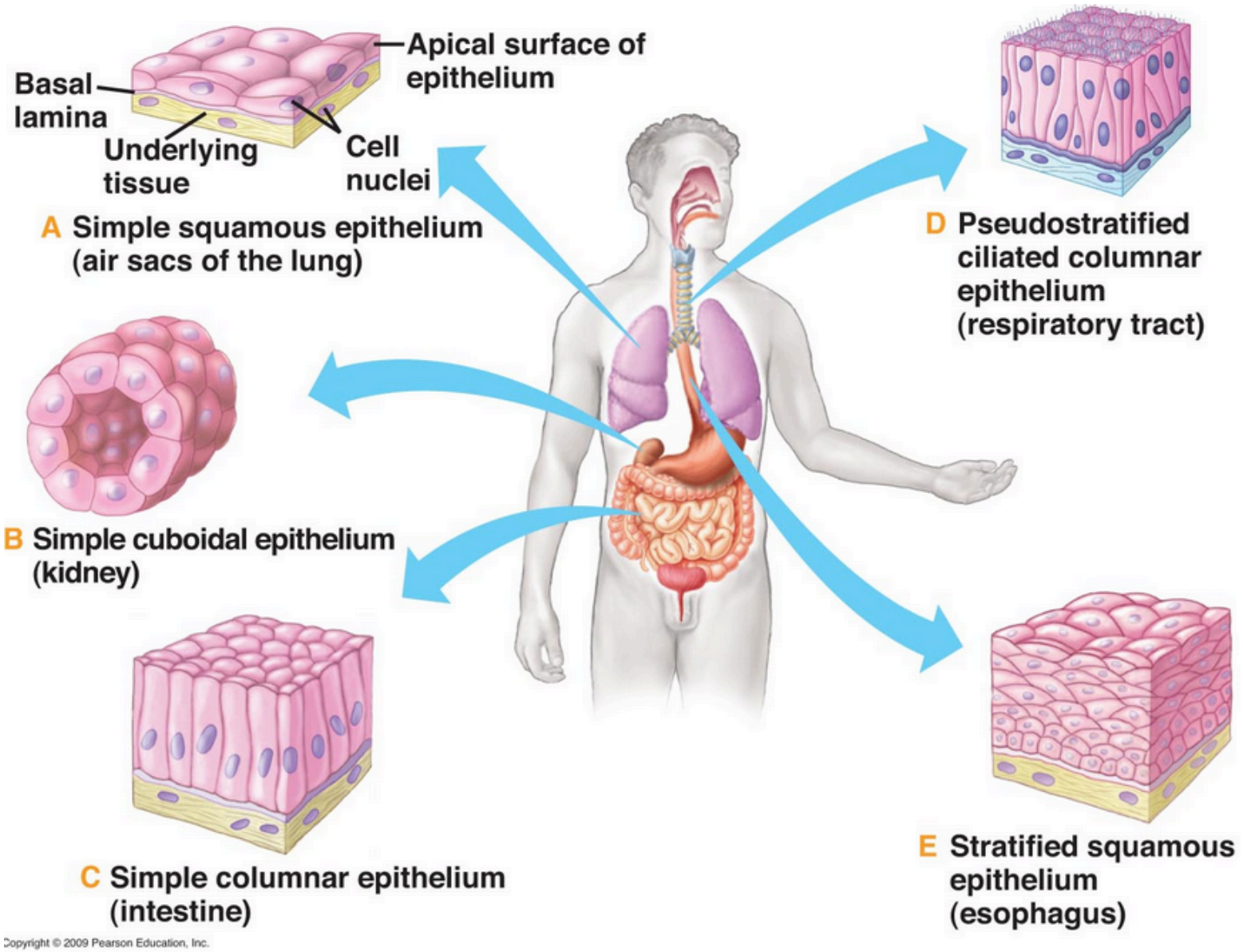
T cells

Endothelial cells

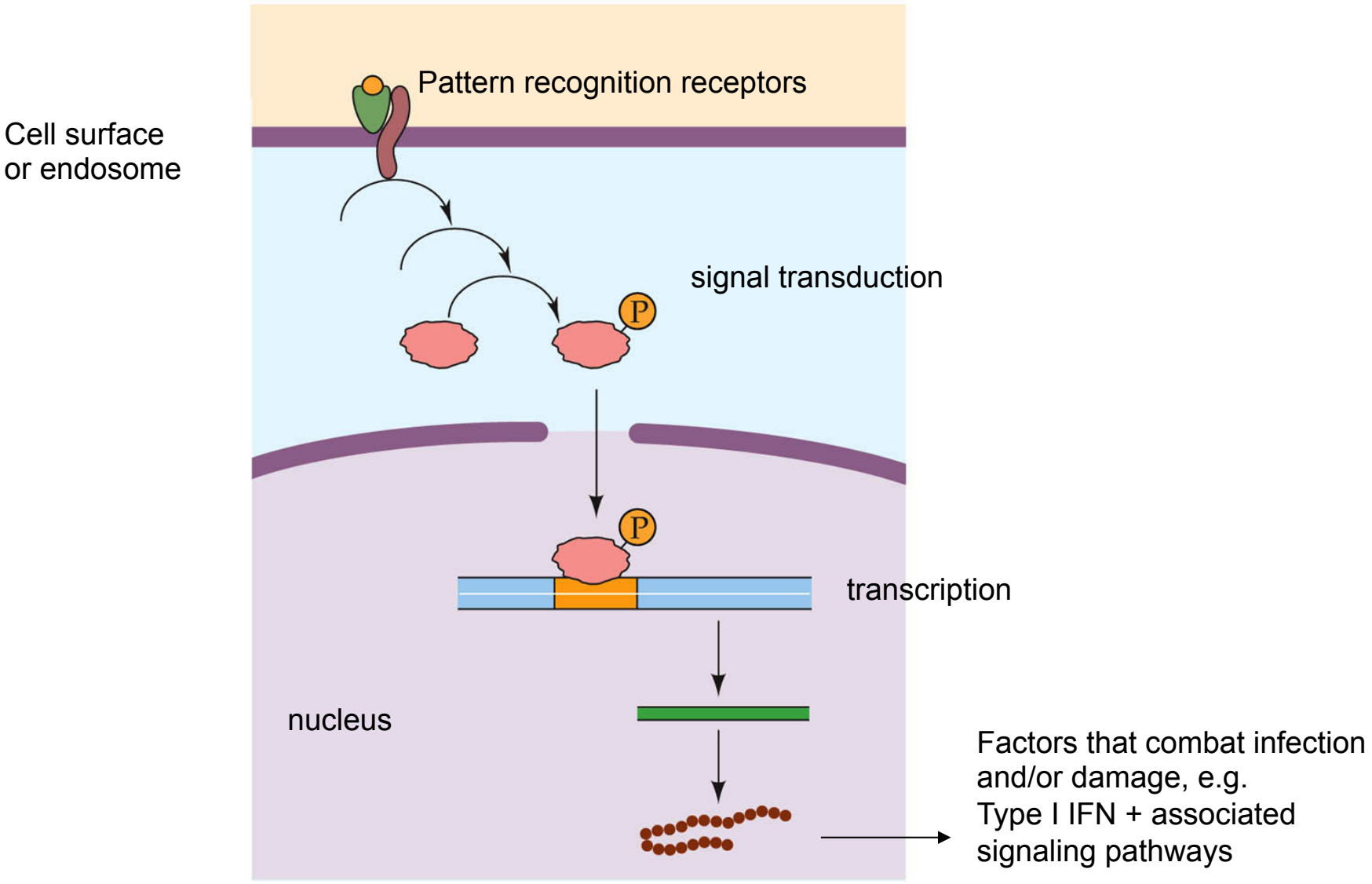
CAFs



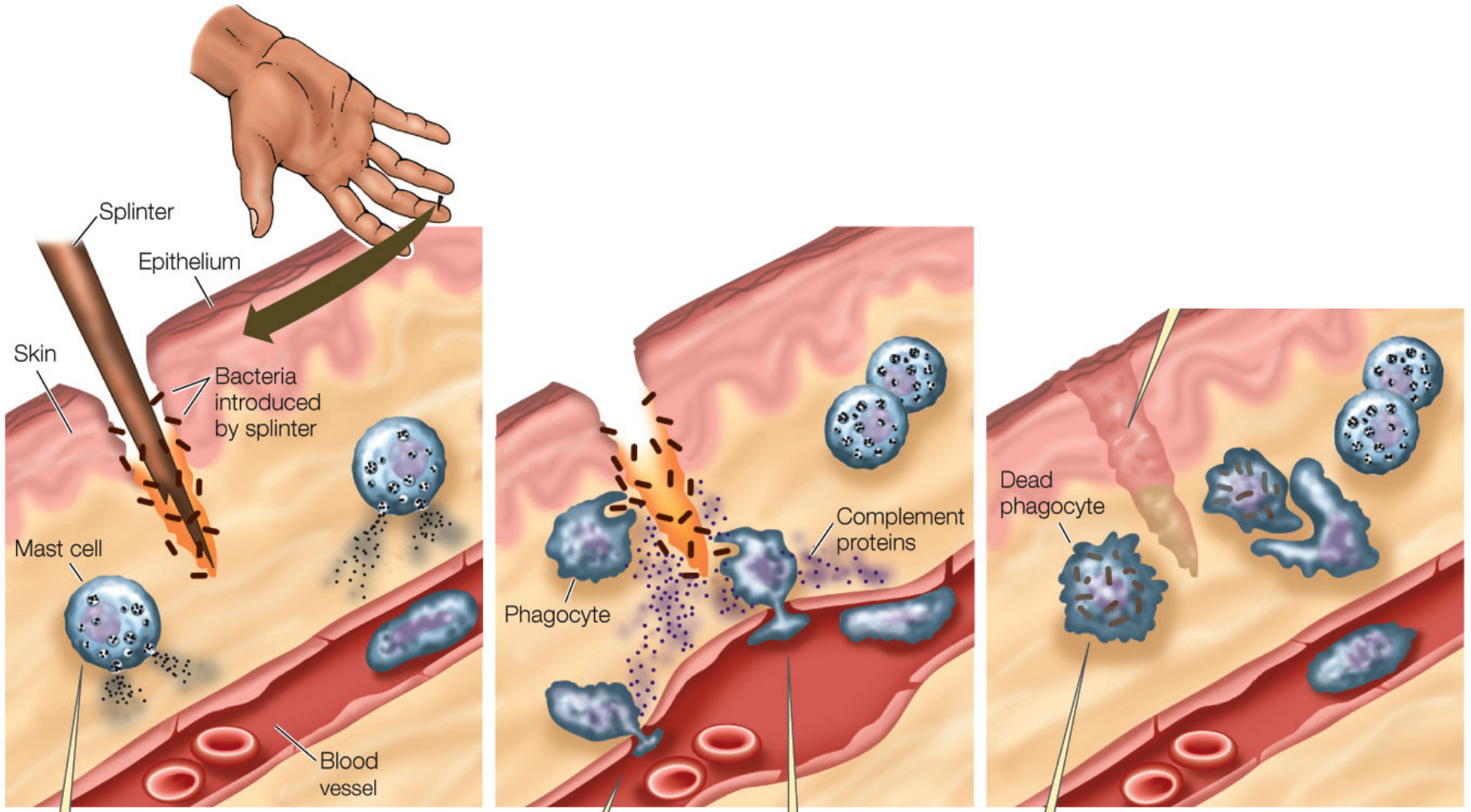
Epithelial cells are the first to be confronted with pathogens or “stress”



Epithelial cells have specific receptor systems to notice pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs)



If epithelial integrity is broken, an innate immune response ensues



Mast cells, macrophages and dendritic cells are activated and start secreting inflammatory mediators

As a result, the vessel wall becomes permeable and neutrophils and other phagocytes, complement and platelets can reach the tissue.

Phagocytes ingest the microbes and dead tissue cells and digest these.

(Platelets excrete factors that promote wound healing).

Key functions of the immune system

1. Cells of the immune system can recognize

“non-self” and “danger”

and thus identify infection and cellular stress

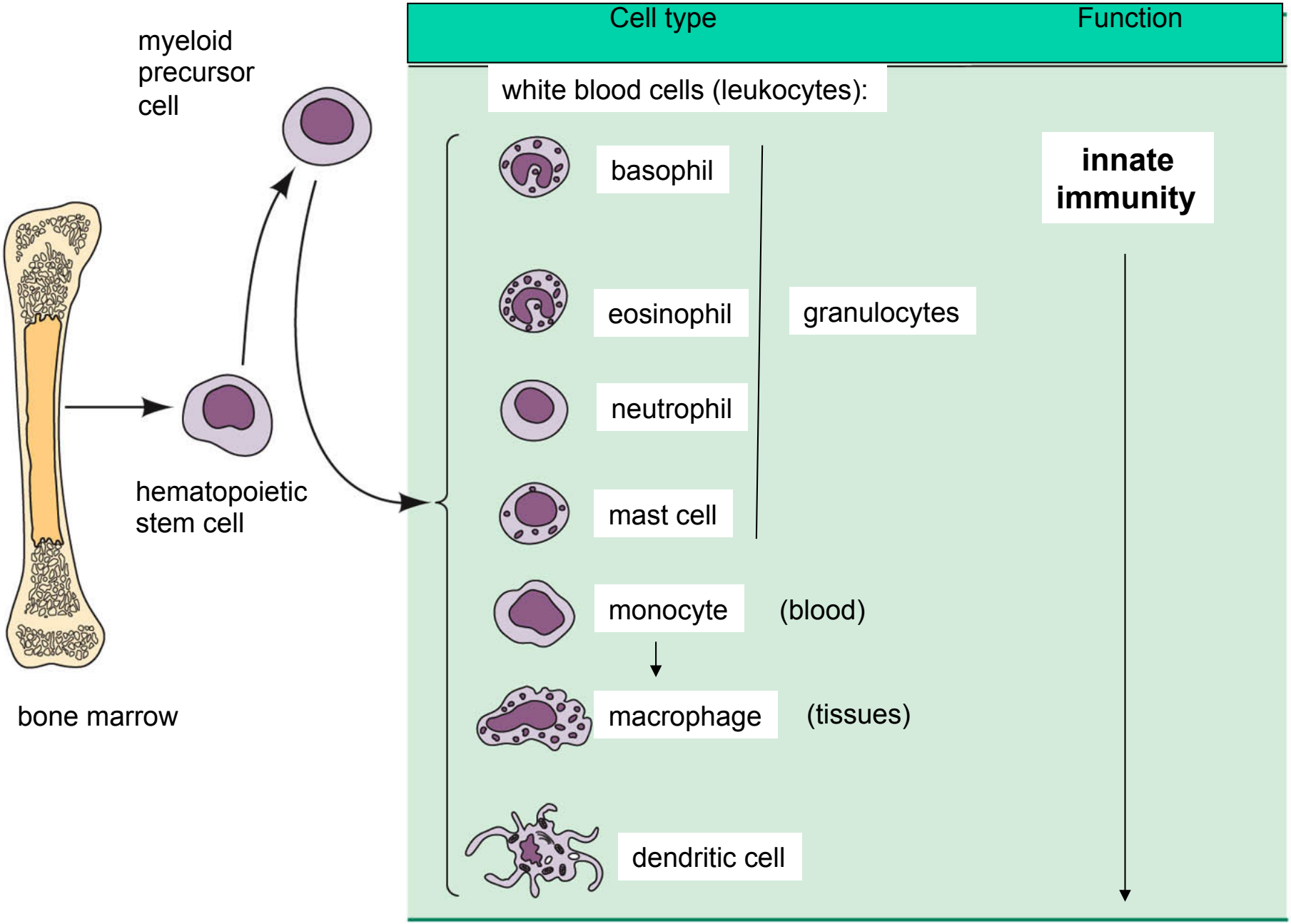
2. Cells of the immune system can exert functions

that neutralize infectious organisms and promote tissue repair

First, cells of the innate immune system react:

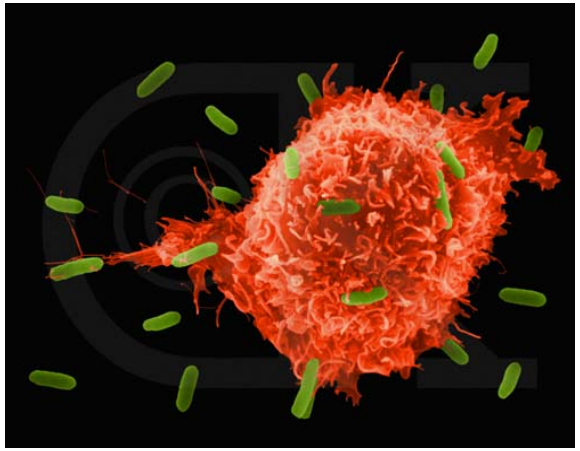
- macrophages
- granulocytes
- dendritic cells

Innate immune cells of the myeloid lineage

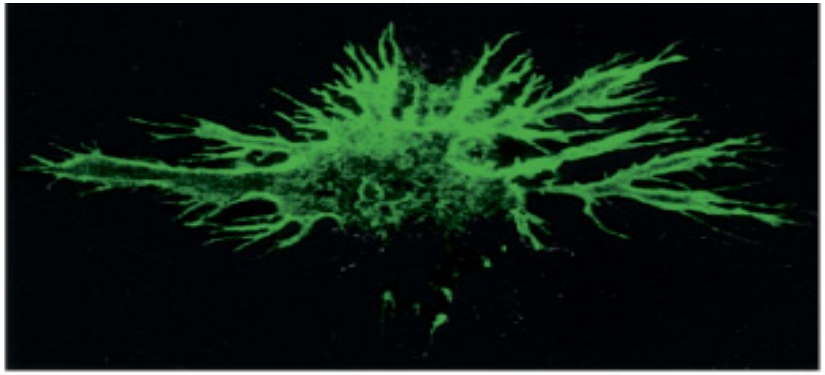


Cells of the innate immune system

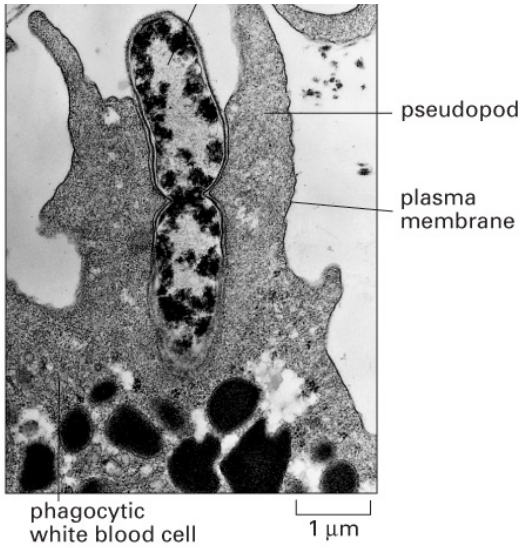
Macrophages



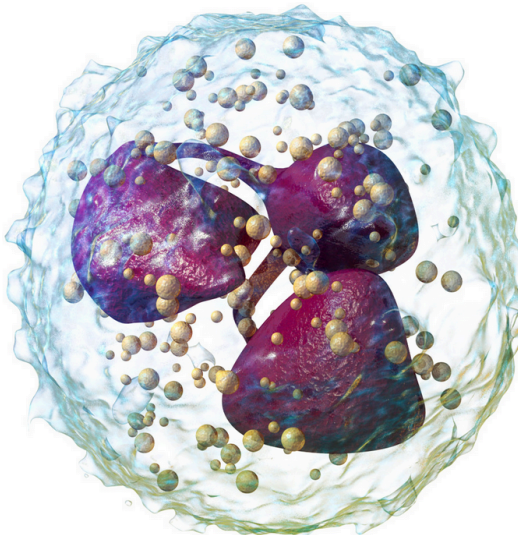
Dendritic cells



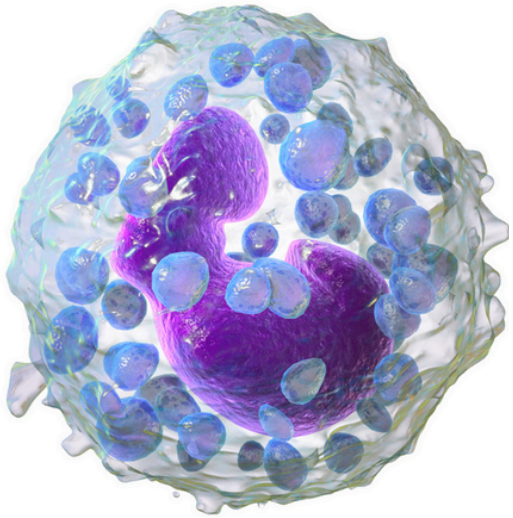
phagocytosis



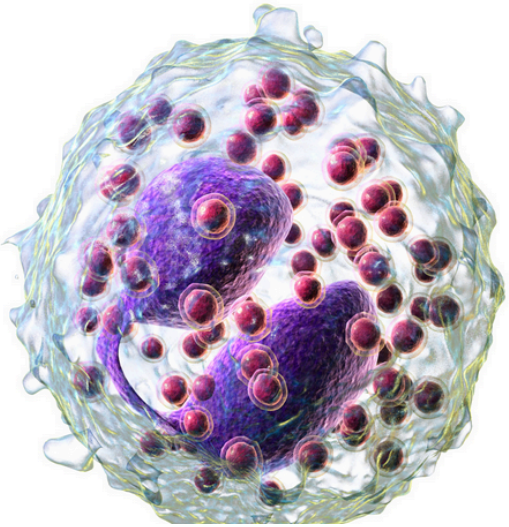
Different types of granulocytes



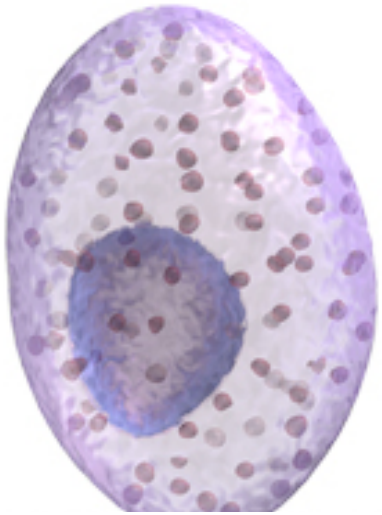
Neutrophil



Basophil



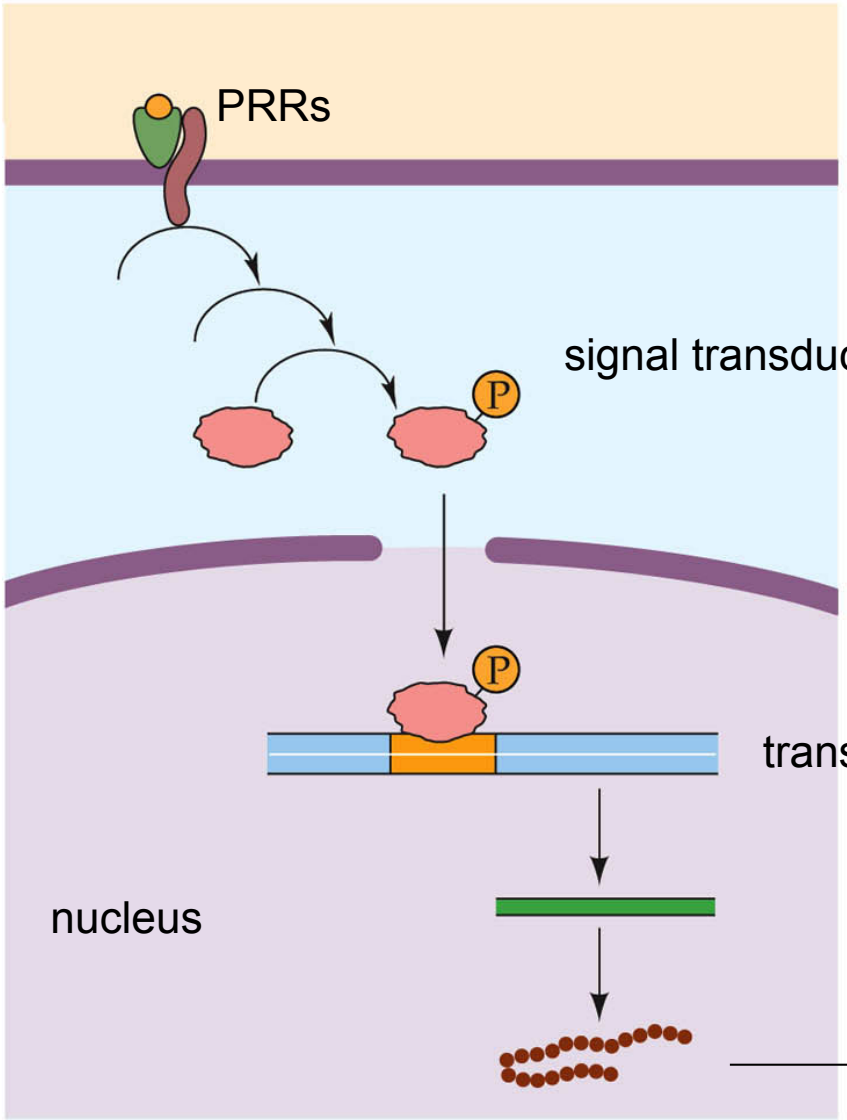
Eosinophil



Mast cell

Innate immune cells also use PRRs
to recognize micro-organisms and “danger”

Cell surface
or endosome



Mediators of:
- phagocytosis
- antimicrobial activity
- inflammation
- repair

TABLE 24–1 Some Pattern Recognition Receptors (PRRs)			
Receptor	**Location**	**Ligand**	**Origin of ligand**
Toll-like receptors (TLRs)			
TLR3	Endolysosomal system	Double-stranded RNA	Viruses
TLR4	Plasma membrane	Bacterial lipopolysaccharide (LPS); viral coat proteins	Bacteria; viruses
TLR5	Plasma membrane	Flagellin	Bacteria
TLR9	Endolysosomal system	Unmethylated CpG DNA	Bacteria, viruses, protozoa
NOD-like receptors (NLRs)			
NOD2	Cytoplasm	Degradation products of peptidoglycans	Bacteria
Retinoic acid-inducible gene 1-like receptors (RLRs)			
RIG1	Cytoplasm	Double-stranded RNA	Viruses
C-type lectin receptors (CLRs)			
Dectin1	Plasma membrane	β-Glucan	Fungi

Table 24-1 Molecular Biology of the Cell 6e (© Garland Science 2015)

First, cells of the innate immune system react:

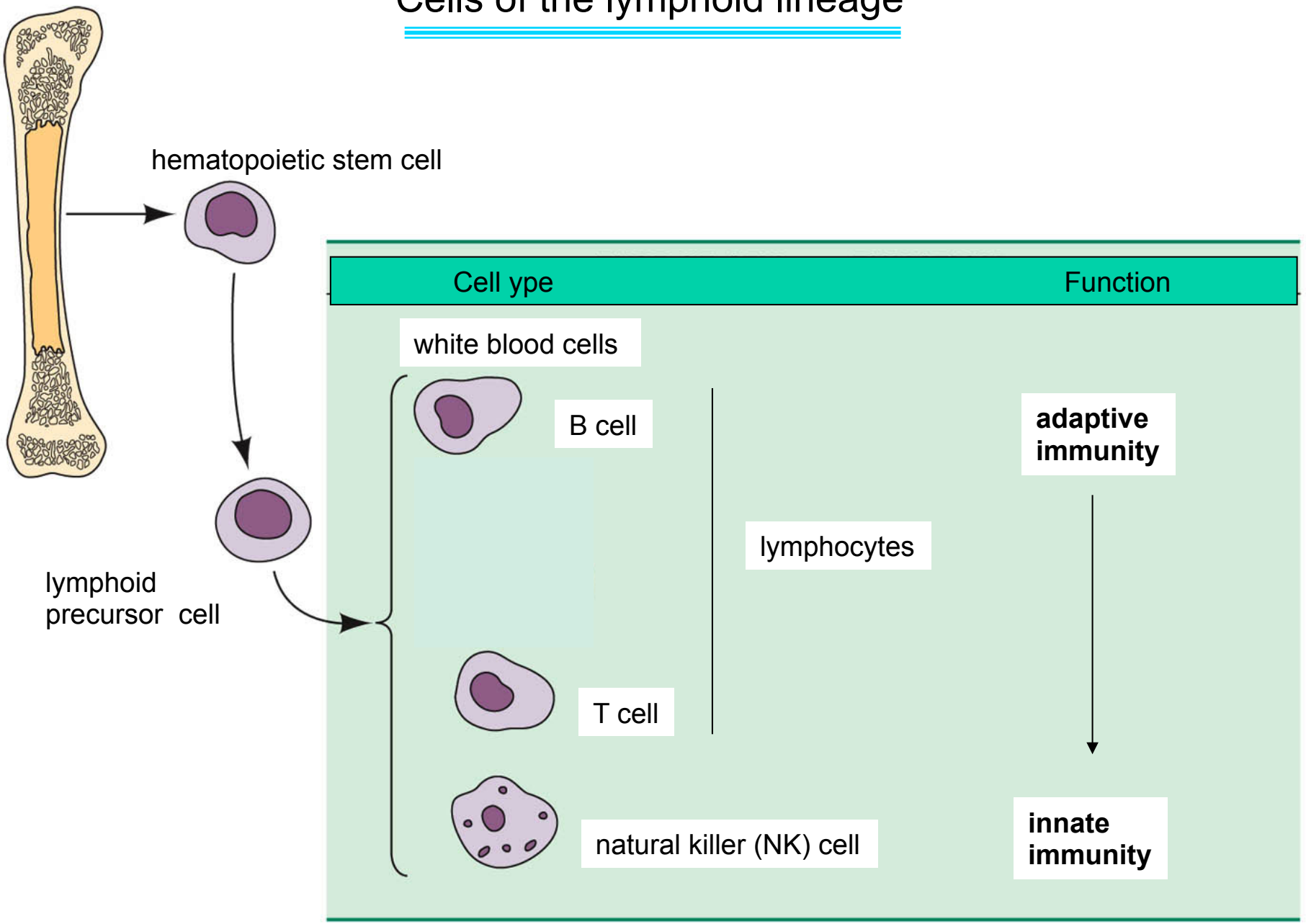
- macrophages
- granulocytes
- dendritic cells

- natural killer cells

Then, cells of the adaptive immune system react:

- T lymphocytes
- B lymphocytes

Cells of the lymphoid lineage



The adaptive immune response

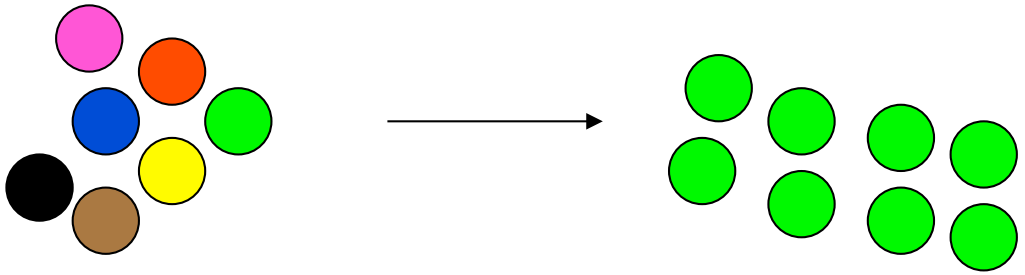
T lymphocytes

B lymphocytes

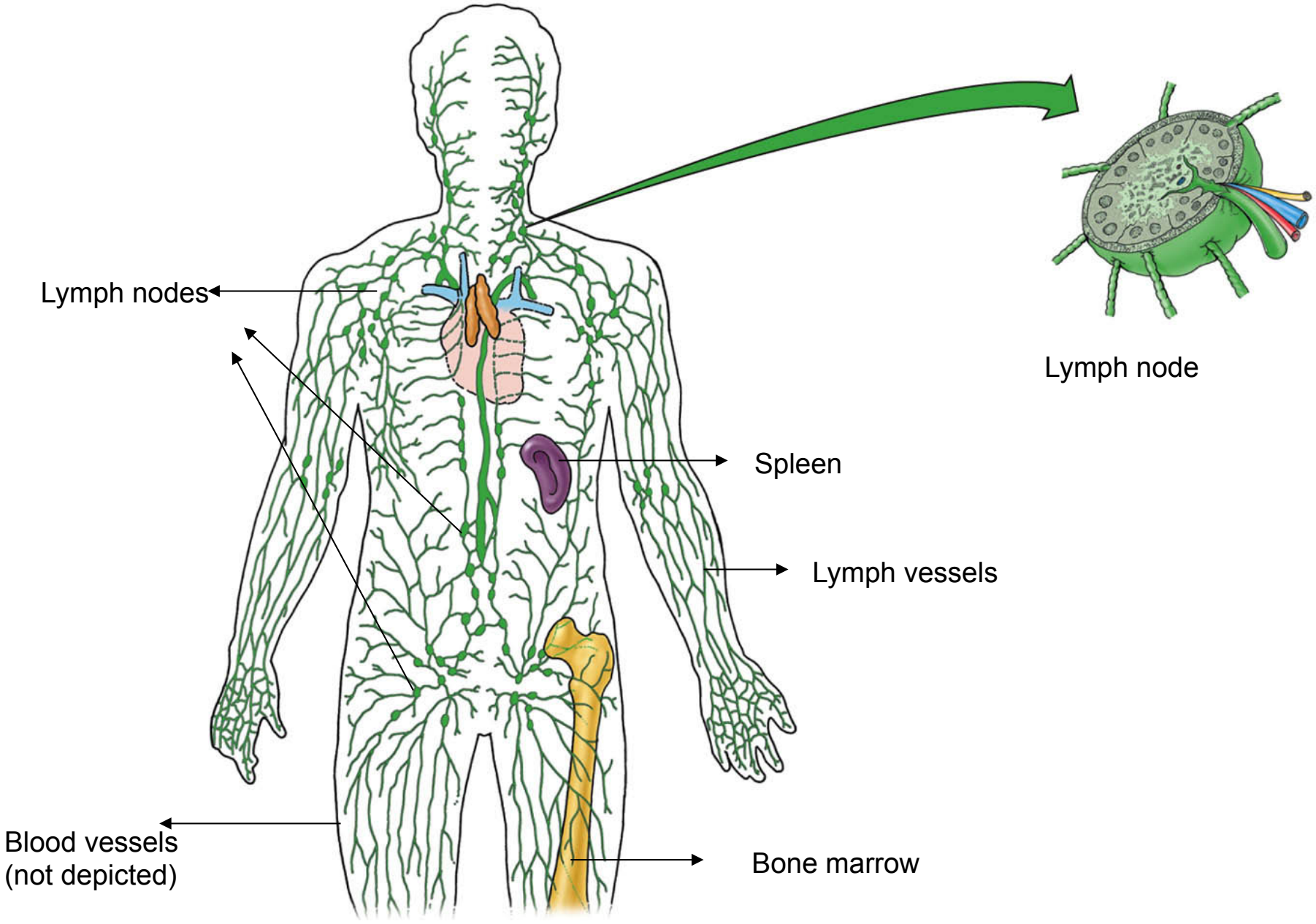
Essence:

- Each individual lymphocyte can recognize something else

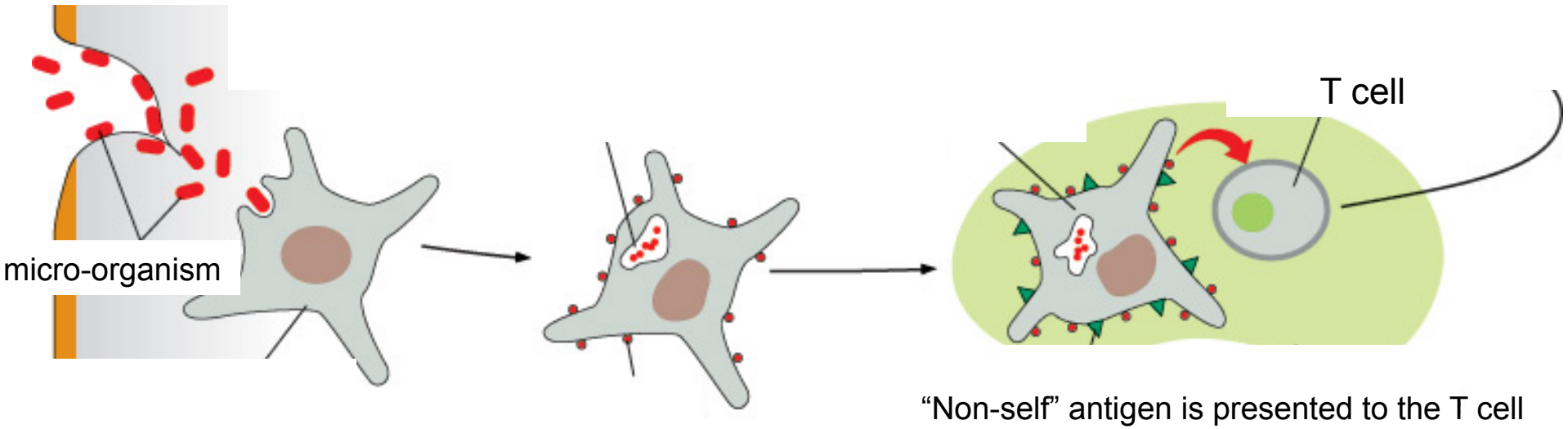
- The lymphocyte that can recognize the infectious organism increases in number



T- and B cell responses takes place in lymph nodes and spleen



Dendritic cells initiate the T cell response



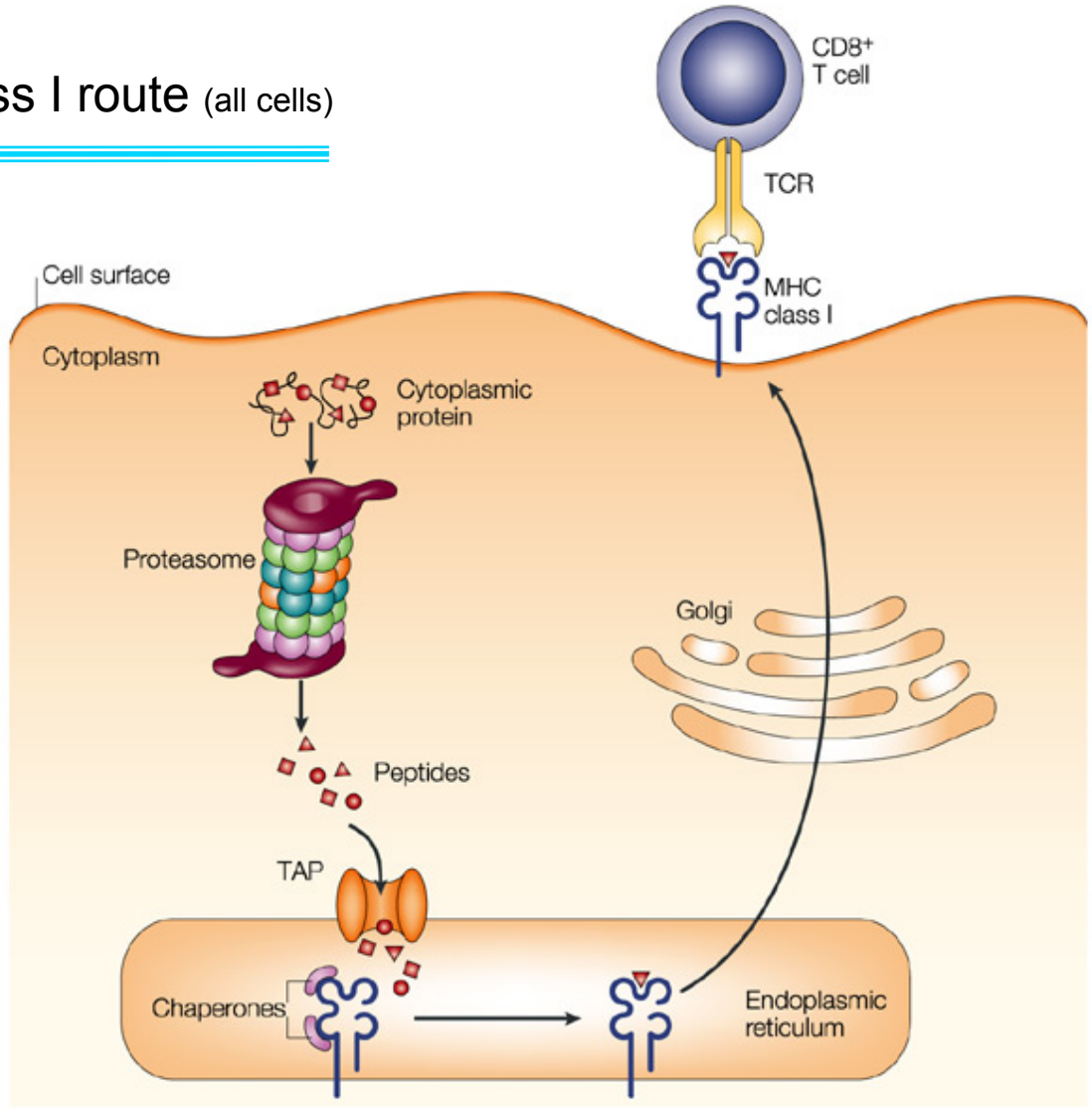
“Non-self” antigen is presented to the T cell

Dendritic cell

Phagocytoses micro-organism and transports it to the secondary lymphoid organs

Antigen presentation

1. The MHC class I route (all cells)

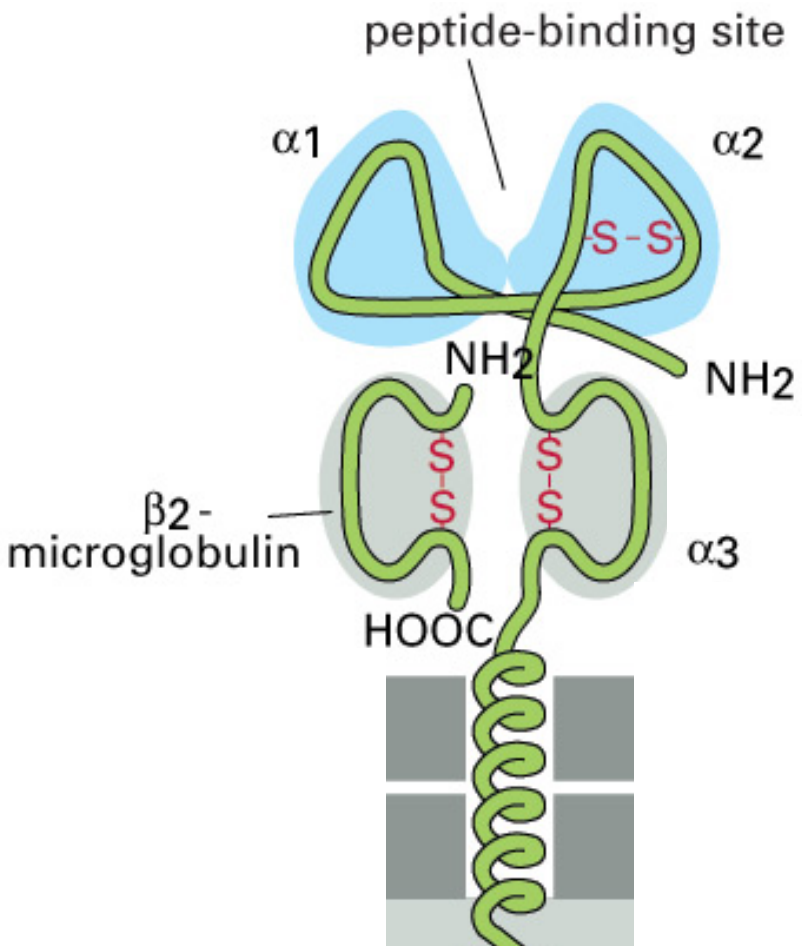


MHC class I

Fragments of cytoplasmic proteins are presented at the cell surface.

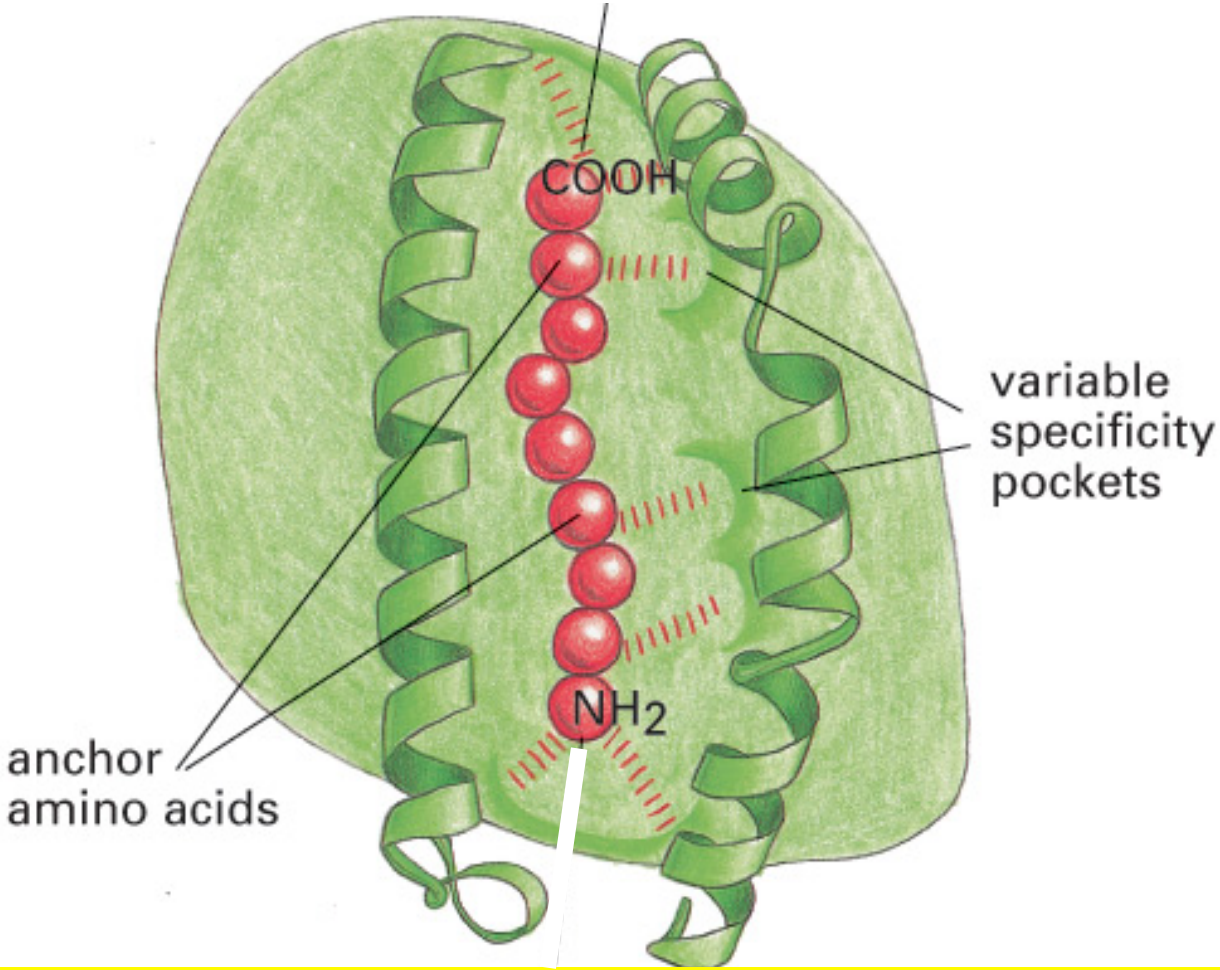
After virus-infection, these are predominantly virus-derived peptides; ordinarily these are “self” peptides.

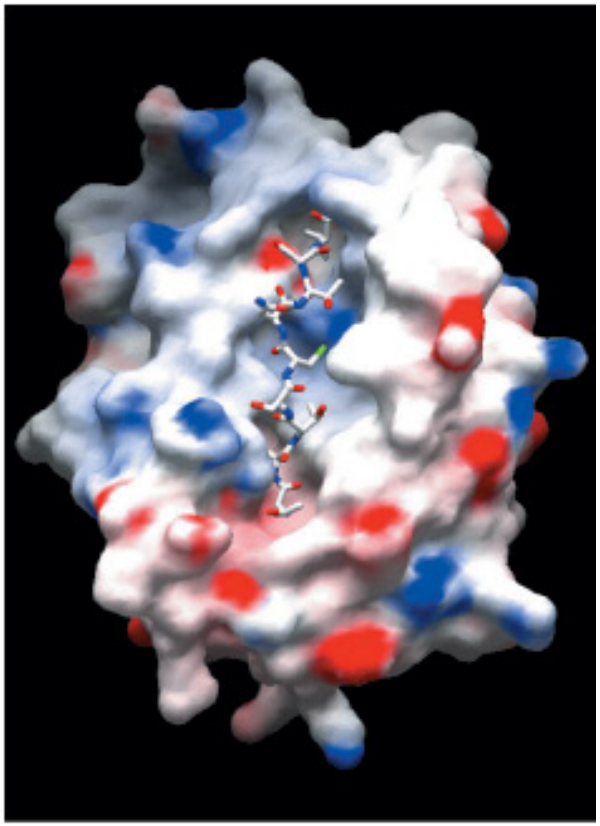
MHC molecules present peptides



MHC (major histocompatibility complex) class I molecule

The peptide binds in de groove of the MHC molecule





This part of the MHC is polymorphic = differs between individuals.

Allows binding of different repertoires of peptides.

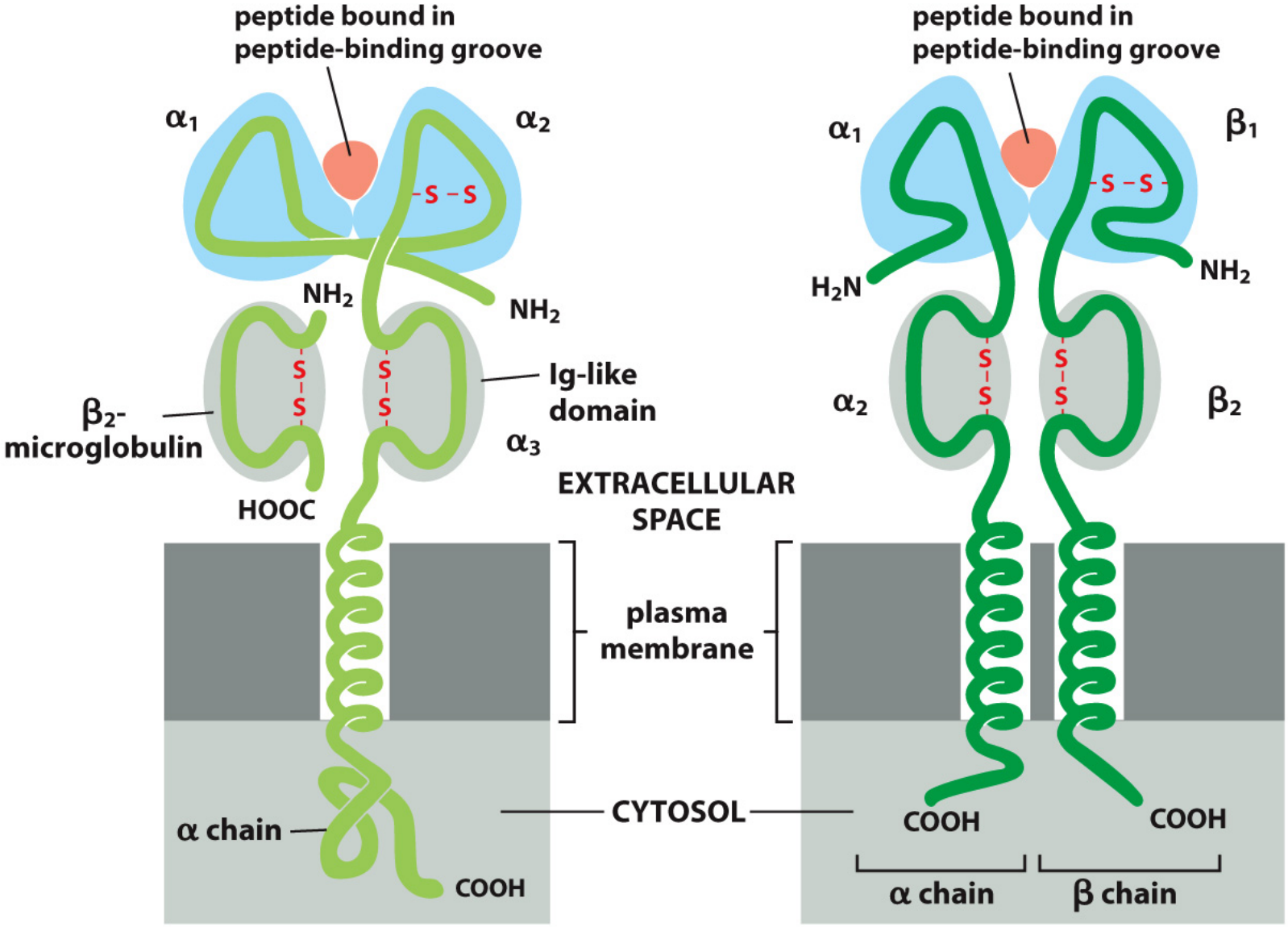
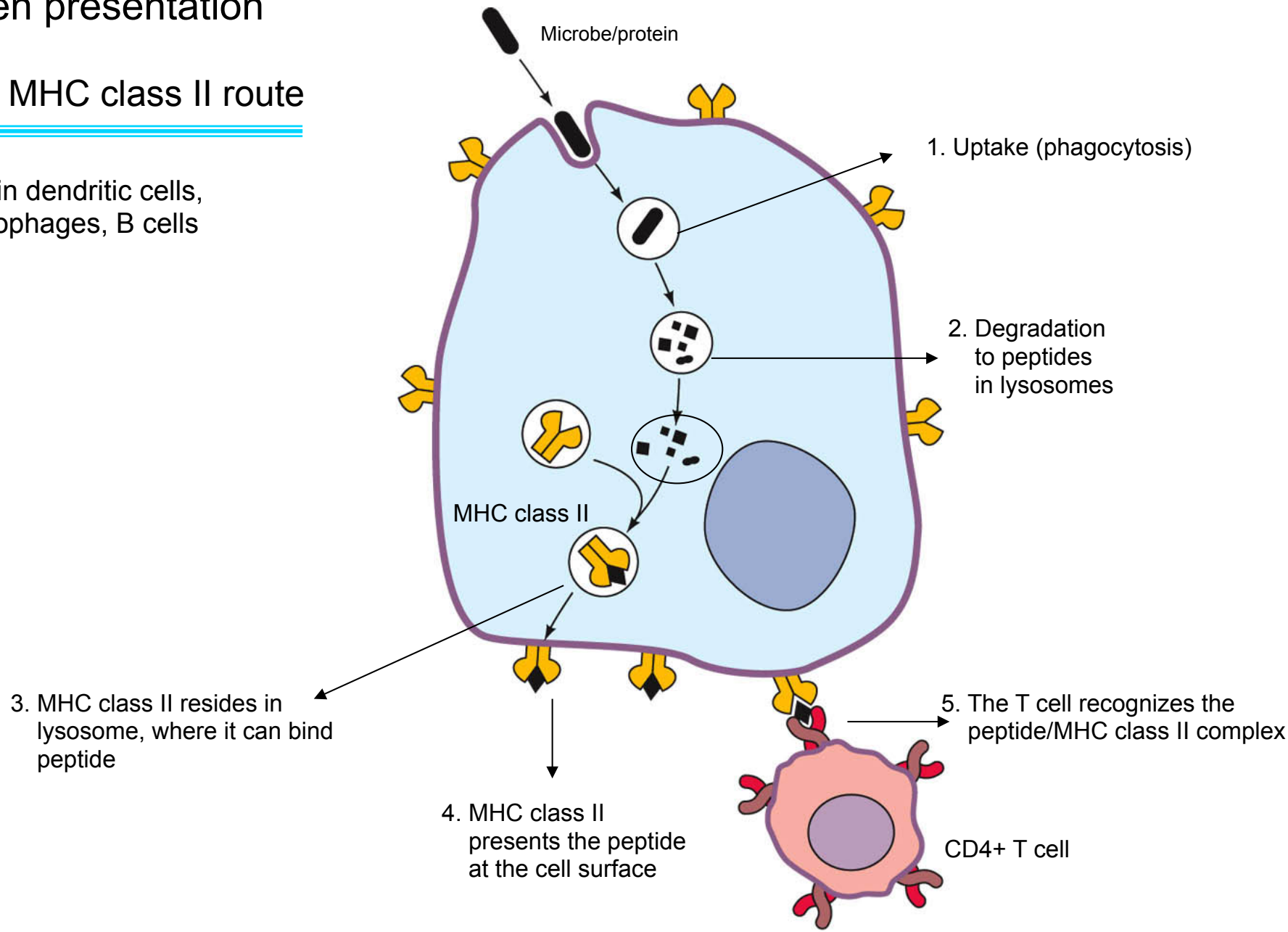


Figure 24-36ab Molecular Biology of the Cell 6e (© Garland Science 2015)

Antigen presentation

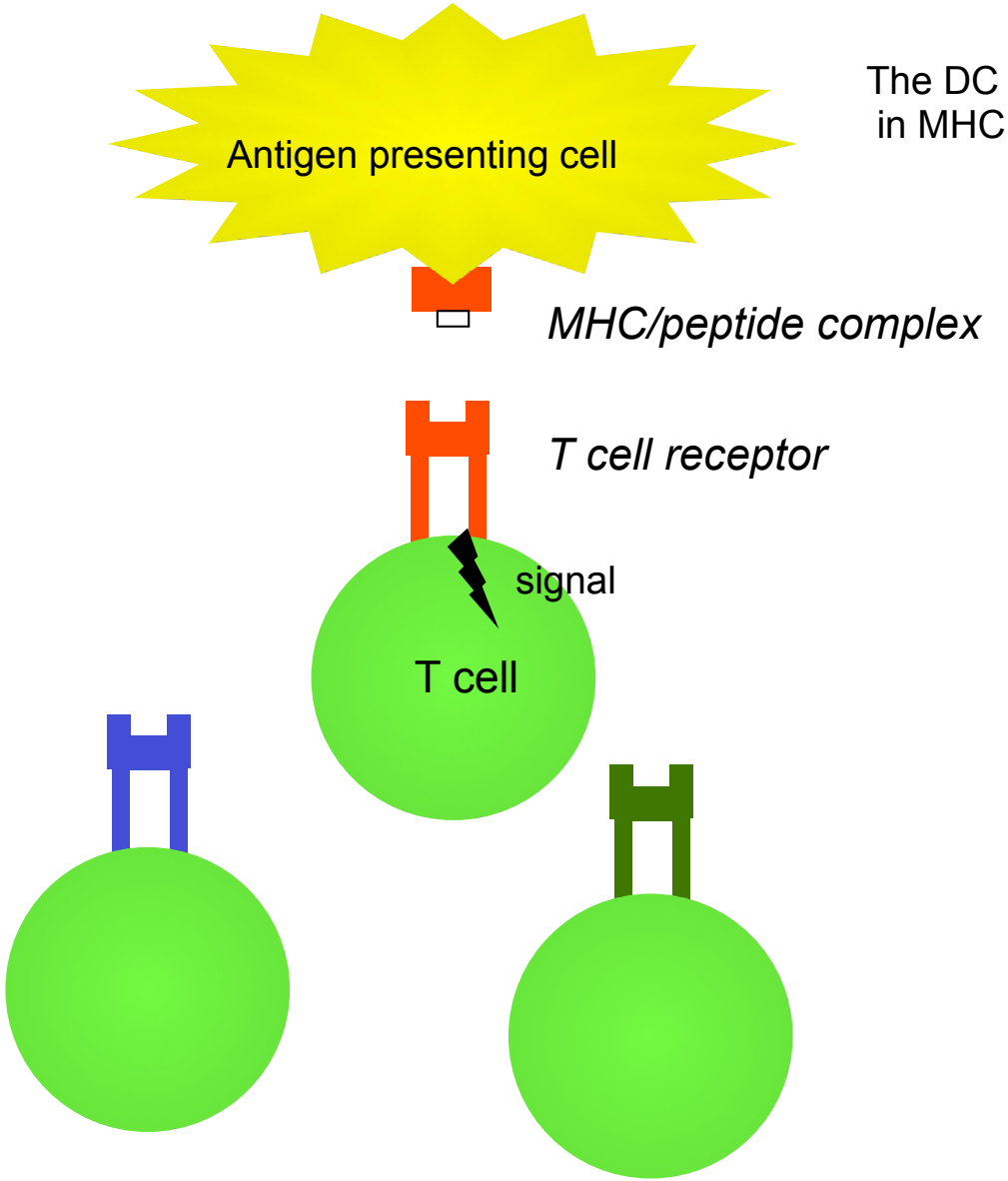
2. The MHC class II route

Only in dendritic cells,
macrophages, B cells



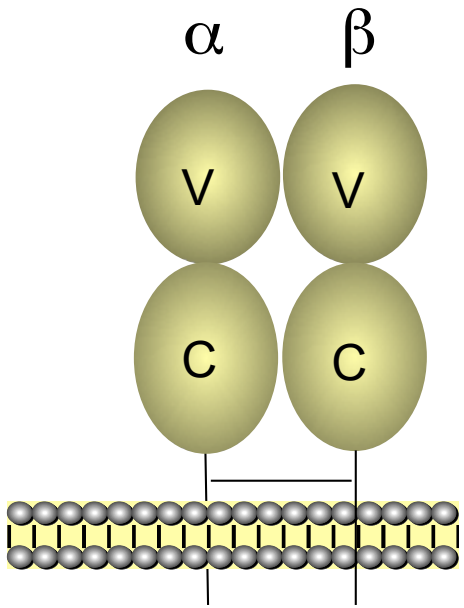
Proteins that are phagocytosed, are broken down in lysosomes and presented at the cell surface by MHC class II.

The T cell response, antigen presentation and recognition



The DC can present endocytosed antigens in MHC class I (cross-presentation)

The T cell recognizes MHC/peptide complex by means of its antigen receptor

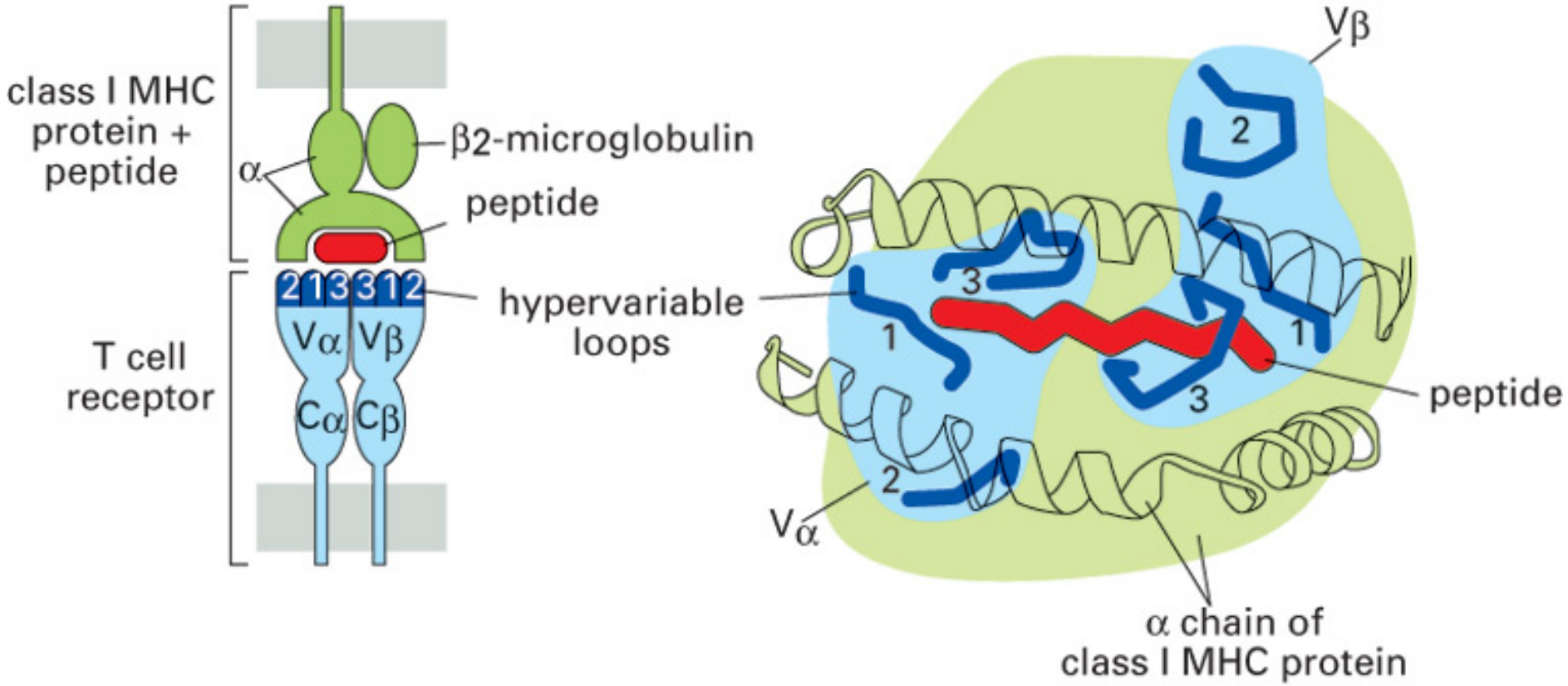


T cell antigen receptor = TCR

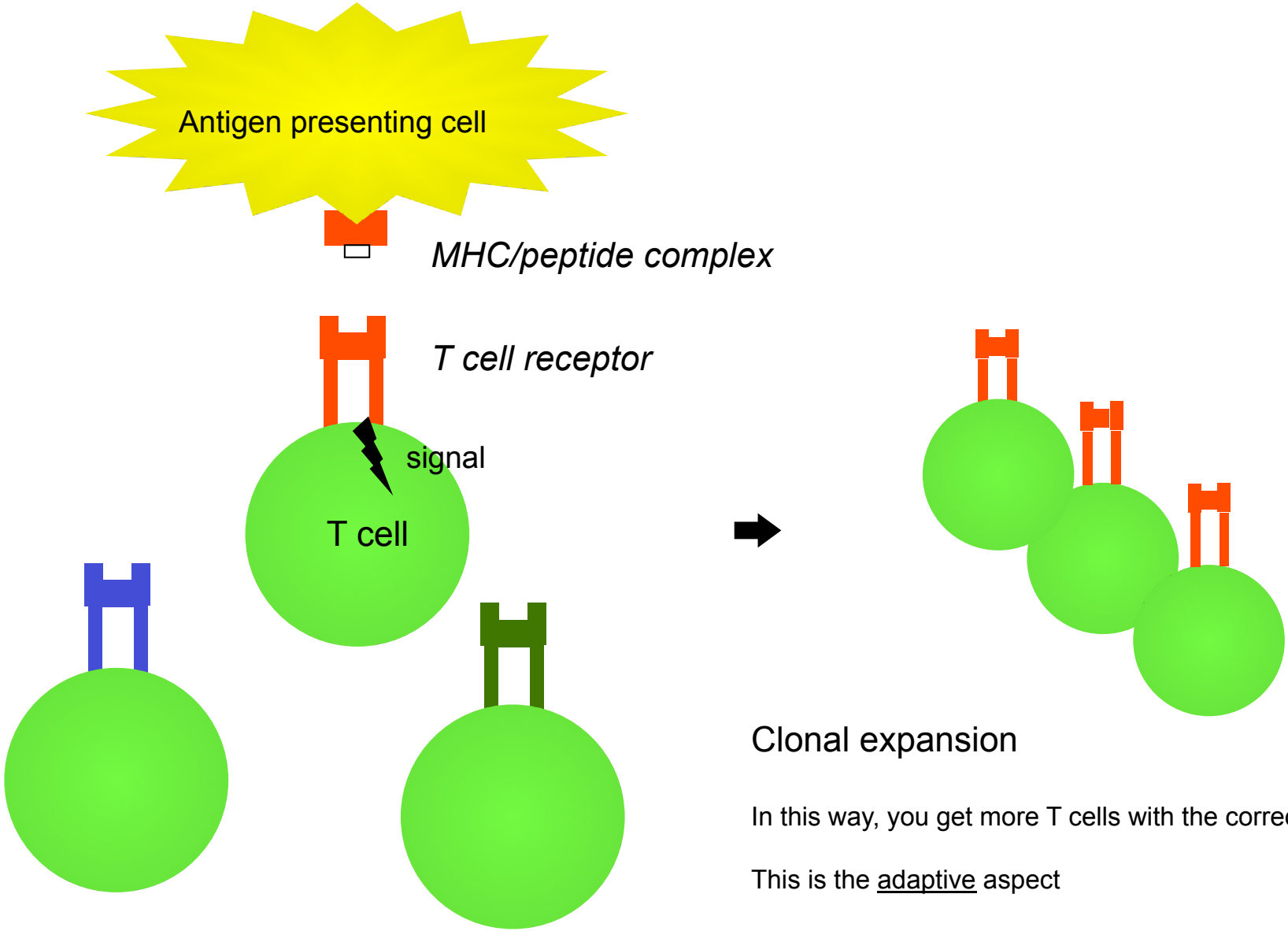
Every T cell has a unique TCR

(variable domains are different from cell to cell)

The TCR recognizes the combination of MHC and peptide



The T cell response, clonal expansion

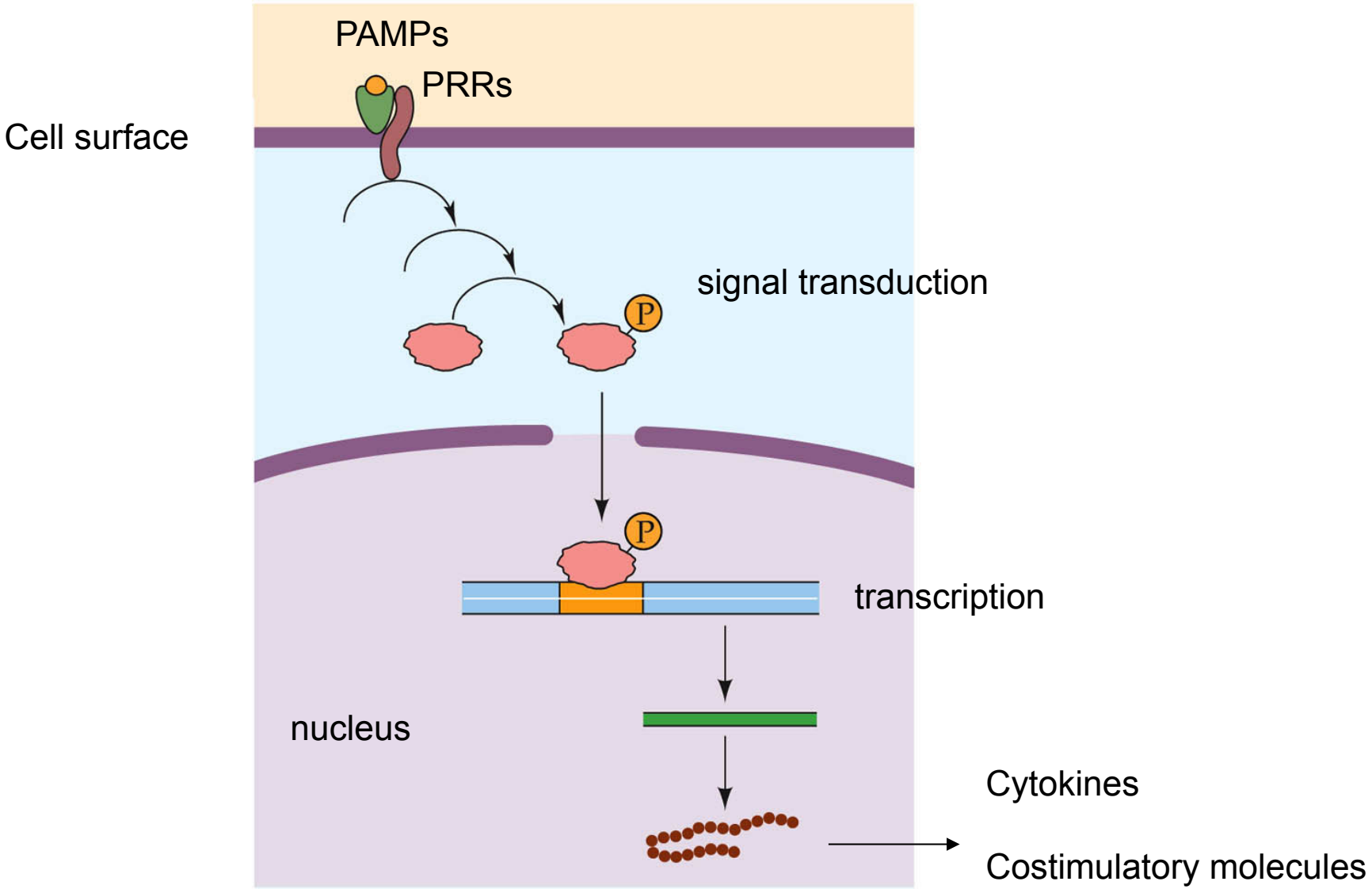


Clonal expansion

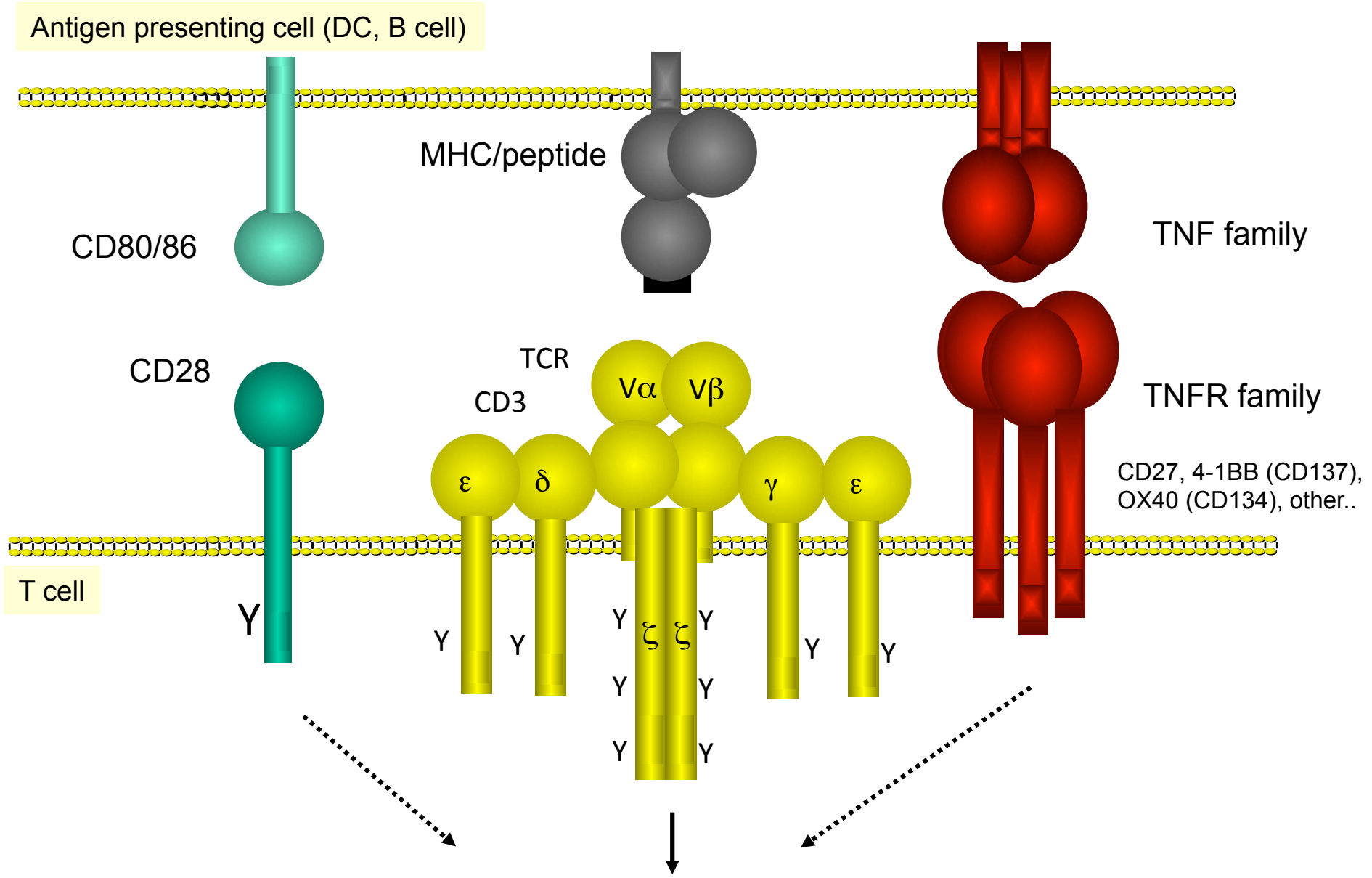
In this way, you get more T cells with the correct specificity

This is the adaptive aspect

When dendritic cells are activated by PRR, they become optimized for T cell priming

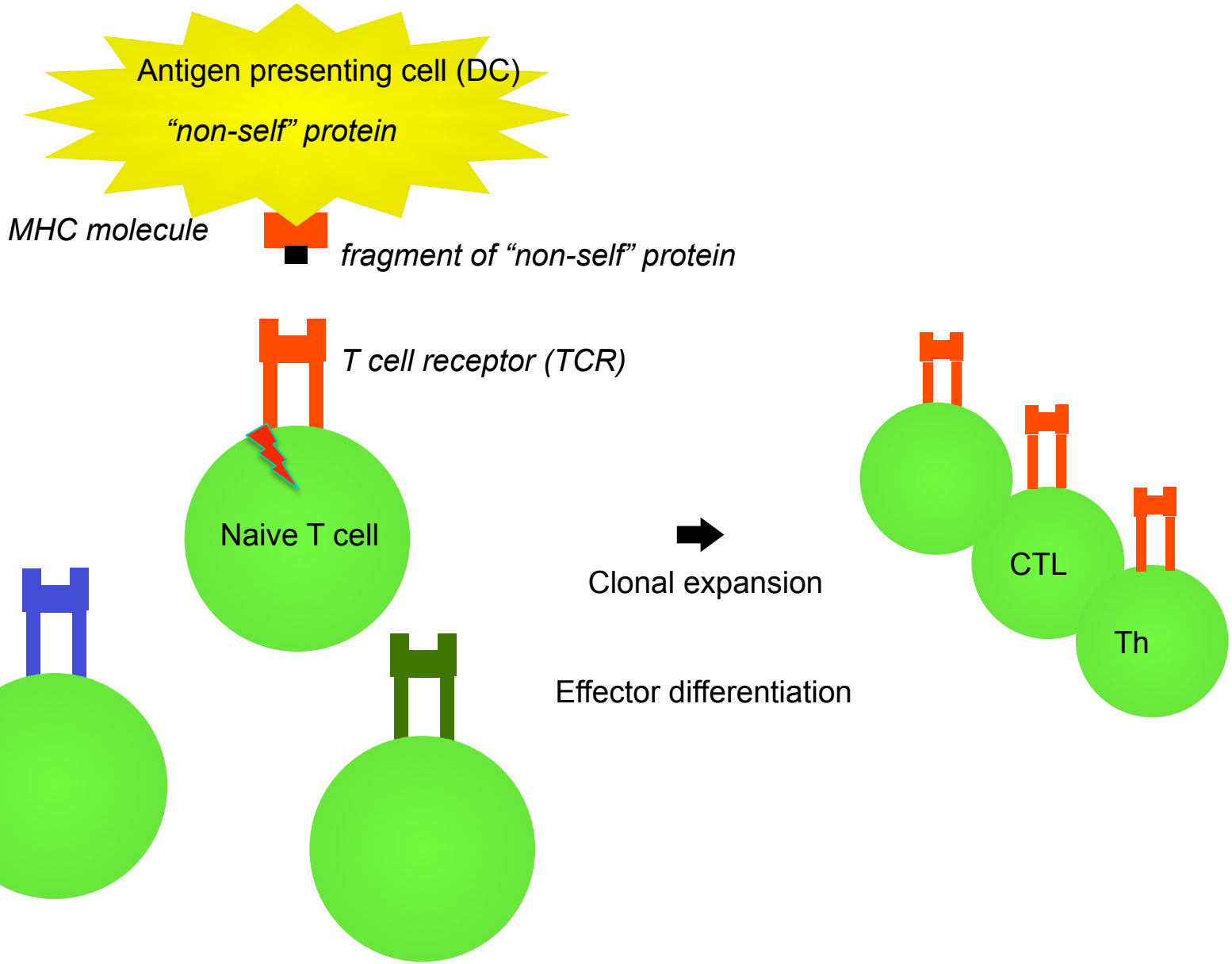


Costimulatory signals are required for T cell priming



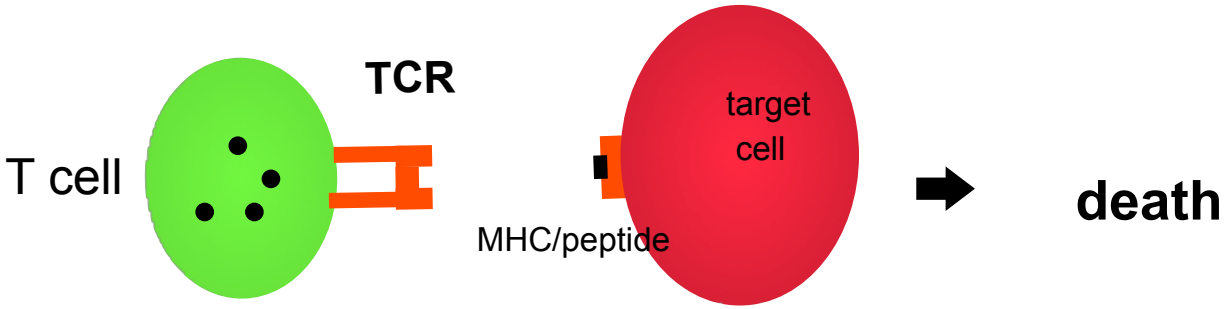
Costimulatory signals promote T cell activation, clonal expansion, effector differentiation

After recognition of **"non-self"** molecules,
T cells make multiple copies of themselves and become effector cells



T cells differentiate during clonal expansion in two types

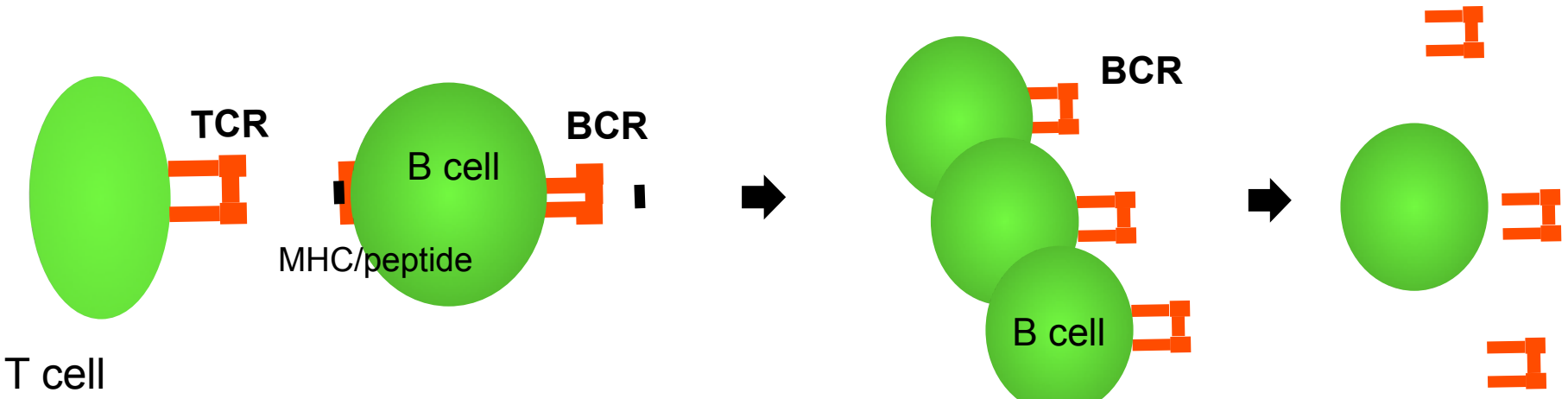
1. Cytotoxic T cells that can kill other cells



2. Helper T cells that can help B cells, CD8+ T cells and innate immune cells to respond

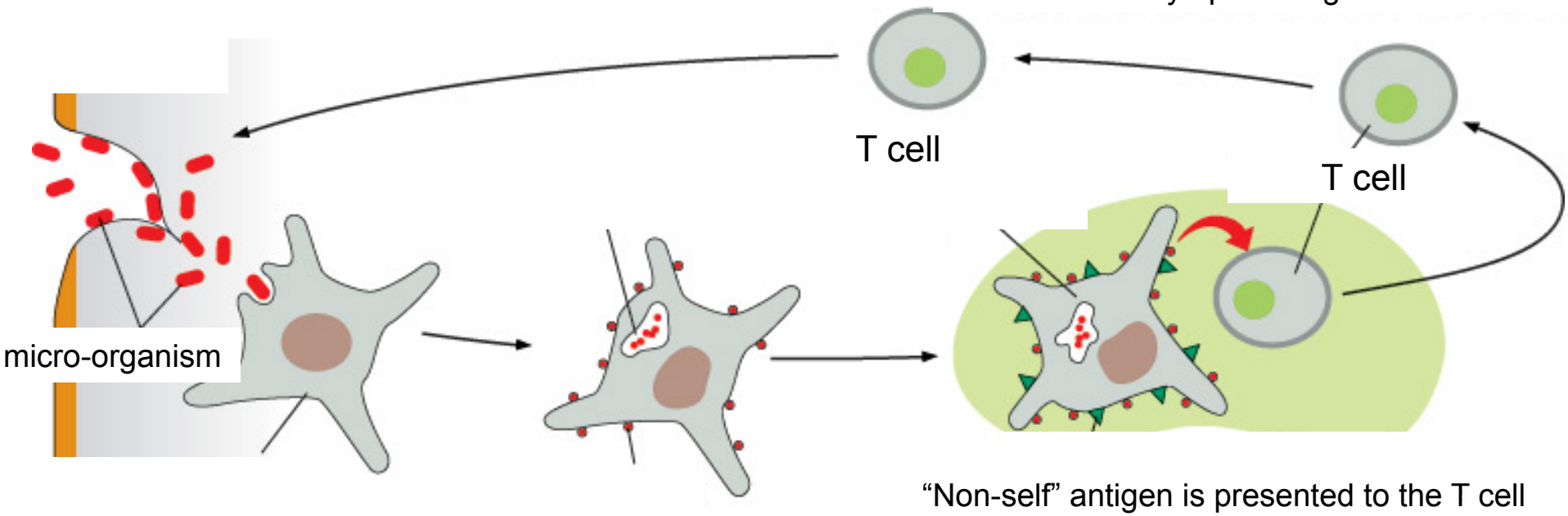
B cells need help from T cells

Helper T cells stimulate B cell expansion and differentiation



The T cell response

T cell multiplies,
differentiates into helper- or cytotoxic cell,
and migrates to the site of infection,
or helps B cells to differentiate
in lymphoid organs



"Non-self" antigen is presented to the T cell

Dendritic cell

Phagocytoses micro-organism and transports it to the
secondary lymphoid organs

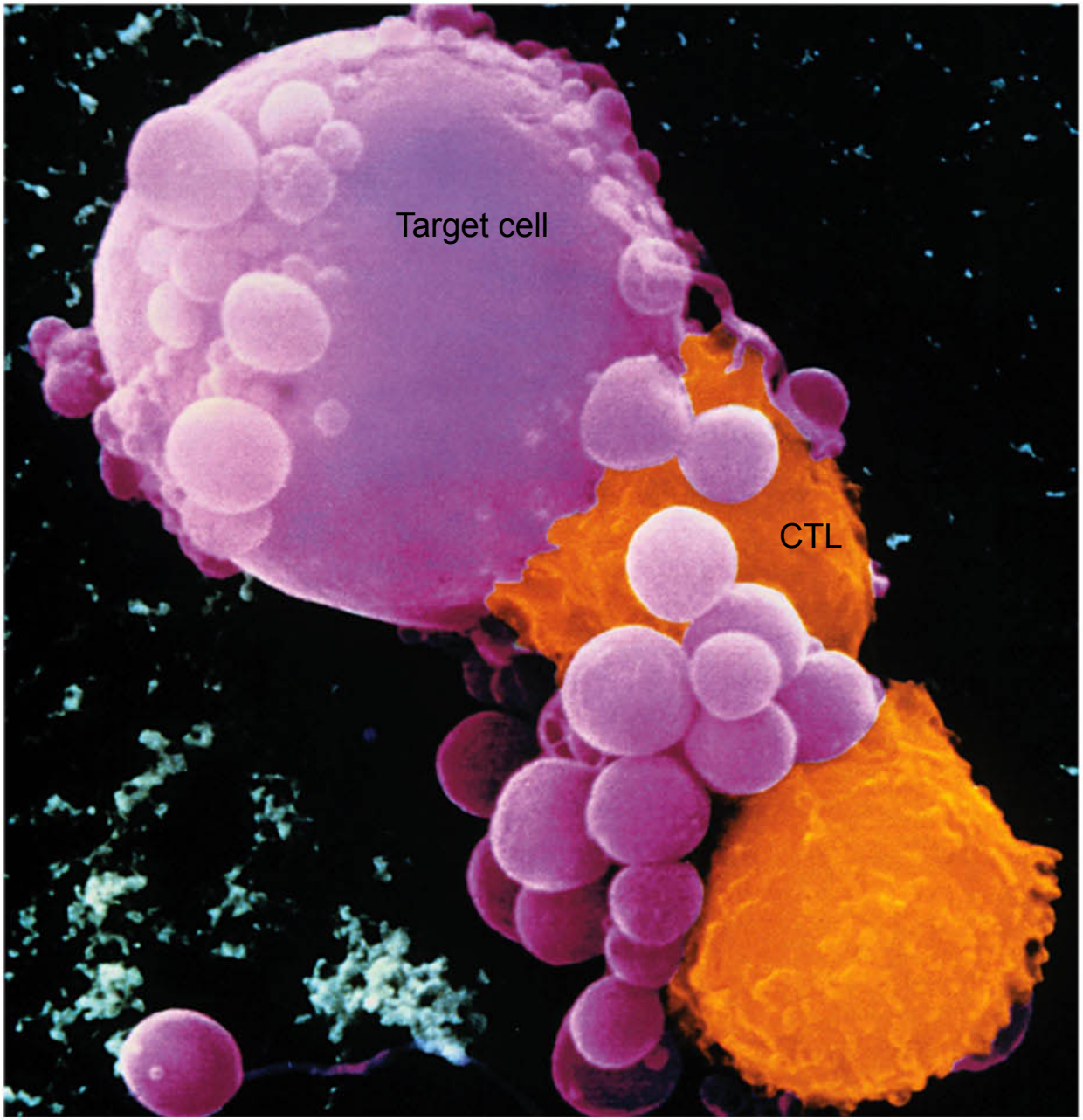
Cytotoxic T cell in action

The CTL needs to recognize the target cell by means of its TCR.

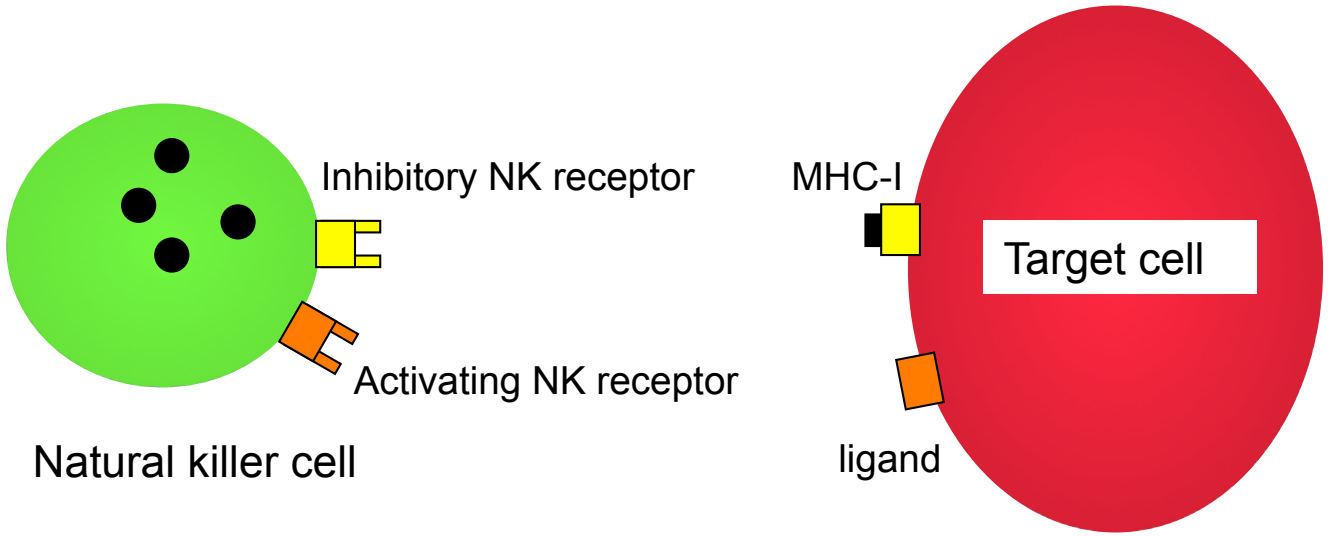
It then induces target cell apoptosis by means of perforin and granzymes, or death ligands (Trail, CD95L).

CD4+ T cells likewise exert their function in synaptic communication after target cell recognition.

CTLs and Th1-type CD4+ effector T cells also secrete IFNγ, TNF, IL-2 upon antigen recognition.

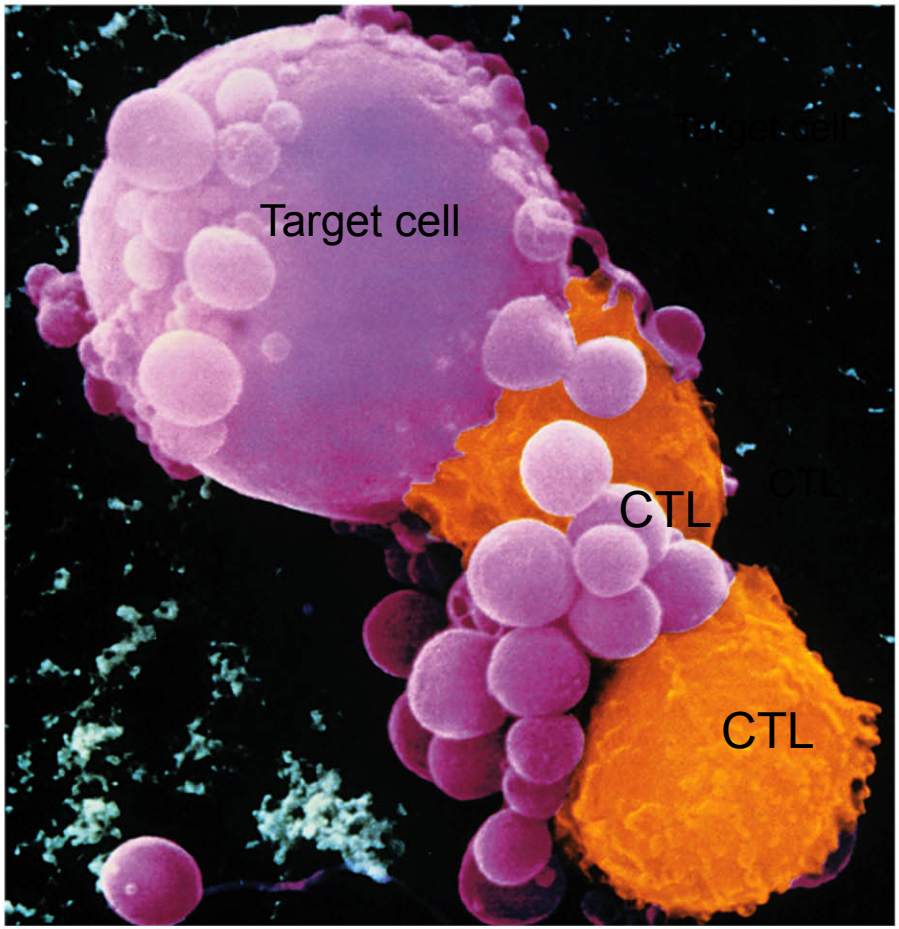


NK cells perceive and react to the absence of classical MHC-I molecules



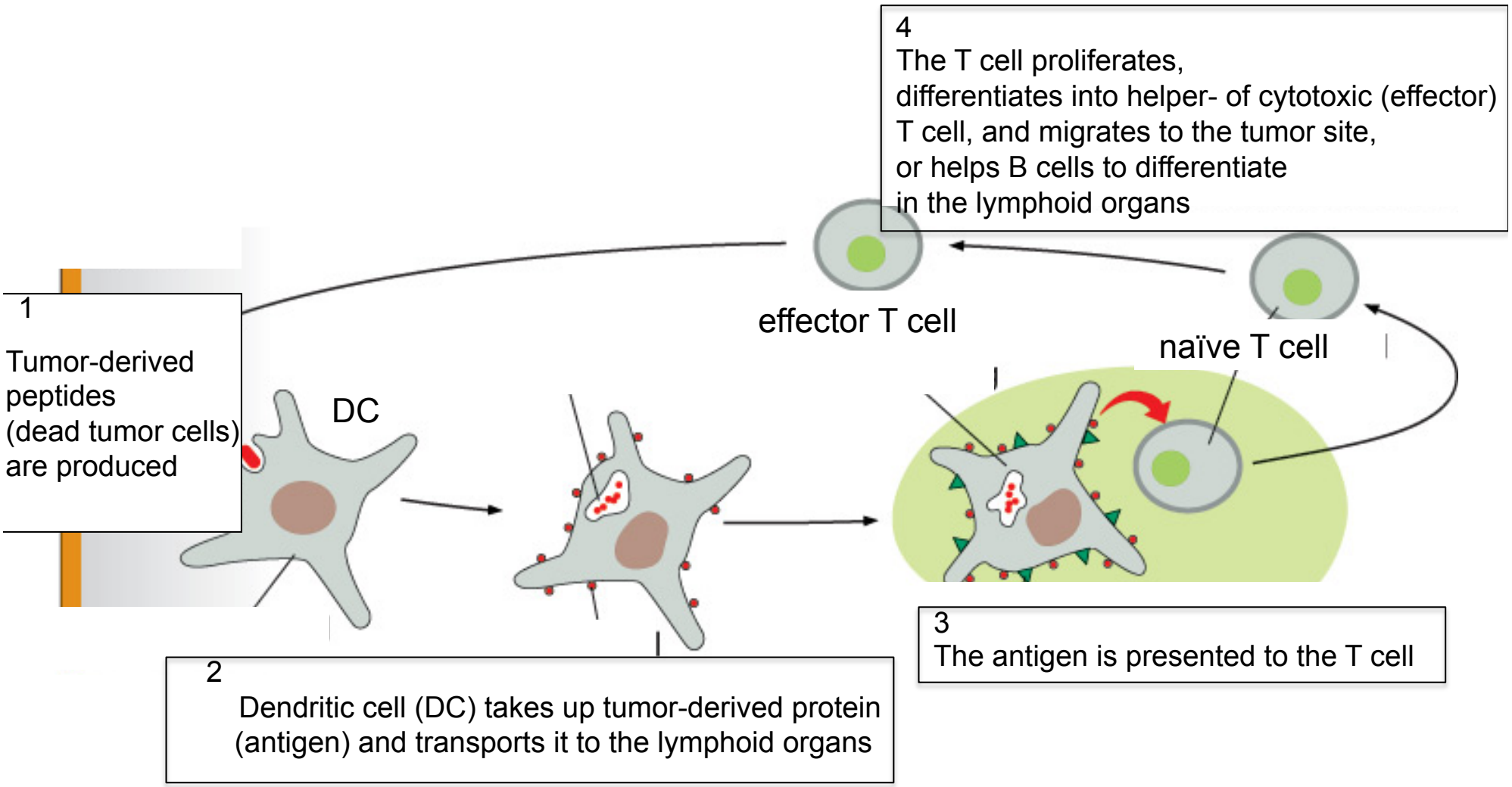
NK cells kill likewise as CTL

The cytotoxic T lymphocyte (CTL) in action



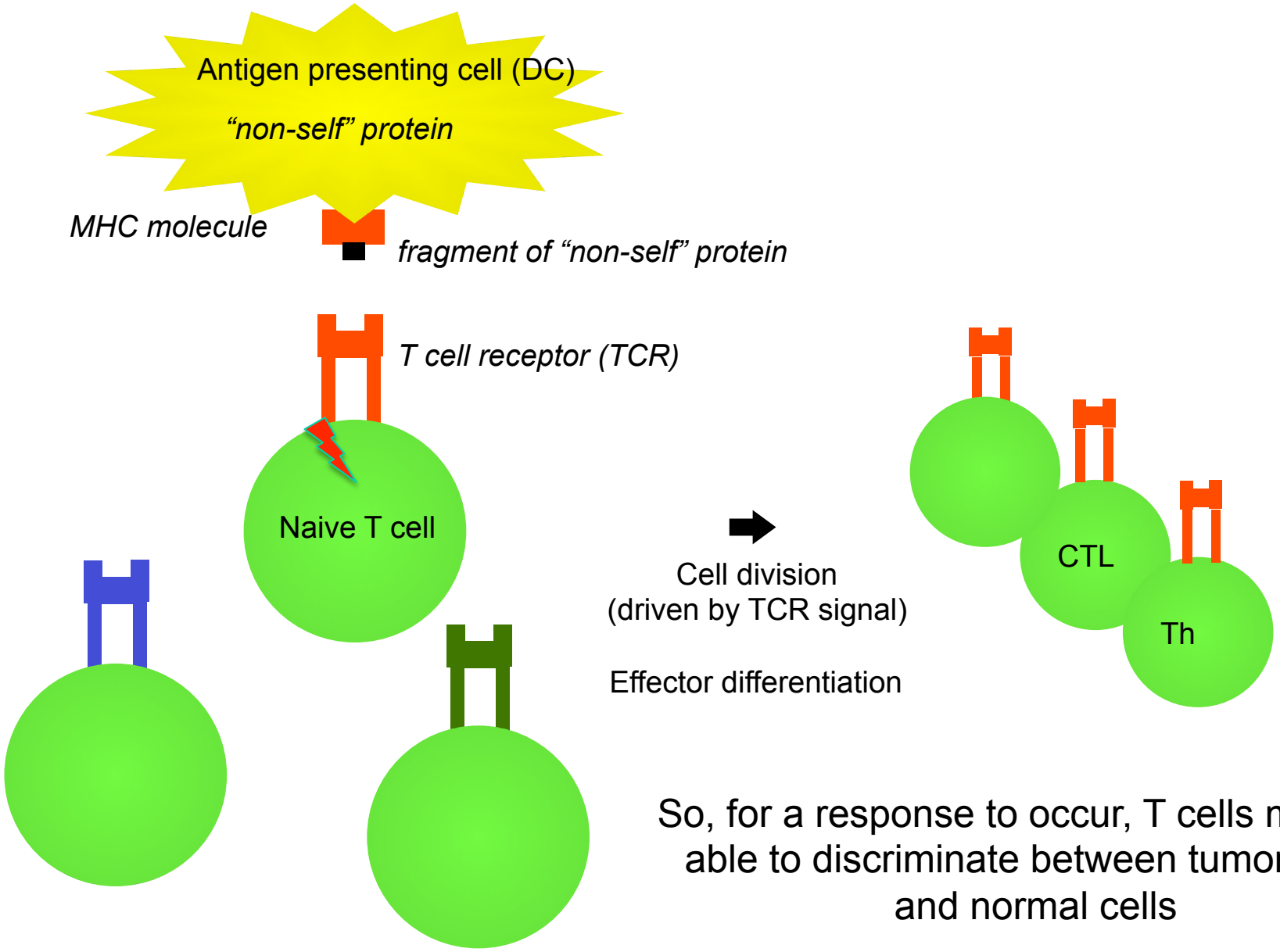
The CTL as ideal weapon to combat metastasized cancer:
specific, effective,
(almost) ubiquitous
& can detect intracellular alterations

Why is the CTL response to cancer shortcoming?



The T cell response against a tumor develops essentially the same as a response to infection

After recognition of **"non-self"** molecules,
T cells make multiple copies of themselves and become effector cells



So, for a response to occur, T cells must be able to discriminate between tumor cells and normal cells

The key bottlenecks in raising a CTL response against cancer

1. Central tolerance

There should be tumor-specific T cells in the peripheral repertoire.
The tumor must offer recognizable (non-self) antigens.

Precursor T cell

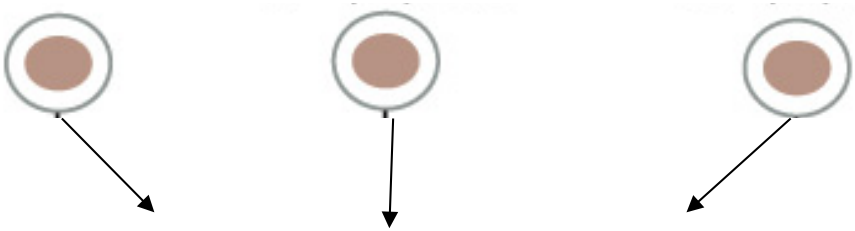
TCR gene rearrangement

No TCR

TCR that cannot recognize peptide/MHC

TCR with high affinity for self-peptide/MHC

TCR with low affinity for self-peptide/MHC



Cell death (apoptosis)

Cell survival and maturation

The selected TCR repertoire is tolerant for "self" antigens

(no autoimmunty)

T cell selection in the thymus

The key bottlenecks in raising a CTL response against cancer

1. Central tolerance

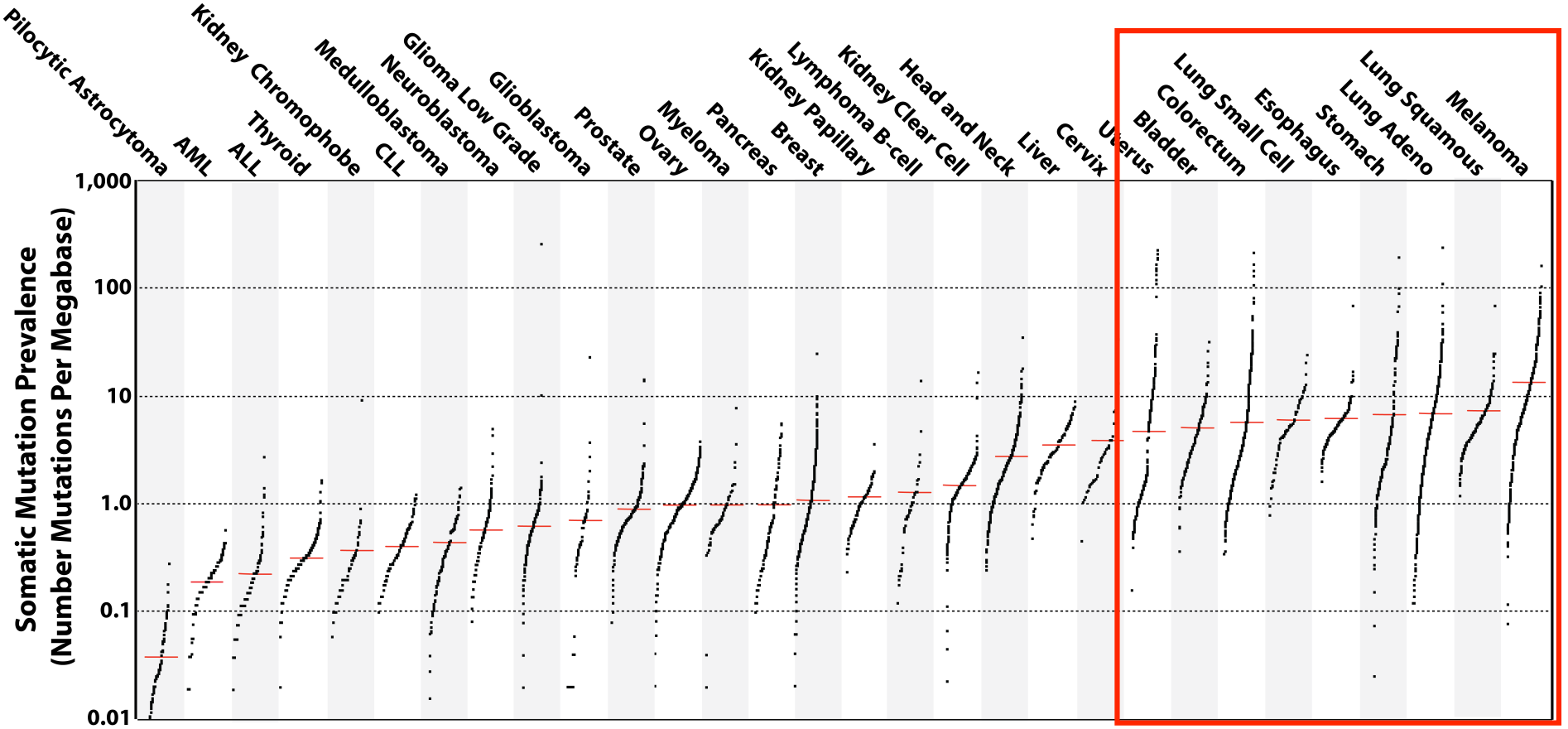
There should be tumor-specific T cells in the peripheral repertoire.
The tumor must offer recognizable (non-self) antigens.

Action: target suitable cancers

Viral proteins
Mutated peptides (neoantigens)
Cancer-testis antigens
Other alterations (e.g. post-translational modifications)

Deep sequencing reveals potential immunogenicity of cancers

but there is more than neo-antigens



Alexandrov et al. Nature, 2013

The key bottlenecks in raising a CTL response against cancer

1. Central tolerance

There should be tumor-specific T cells in the peripheral repertoire.
The tumor must offer recognizable (non-self) antigens.

2. Tumor-associated immunosuppression

CTLs are suppressed in the tumor-microenvironment.

3. Peripheral tolerance

The tumor must activate dendritic cells. This usually does not happen.

Immunosuppression in the tumor micro-environment

Tumor cells

Macrophages

Neutrophils

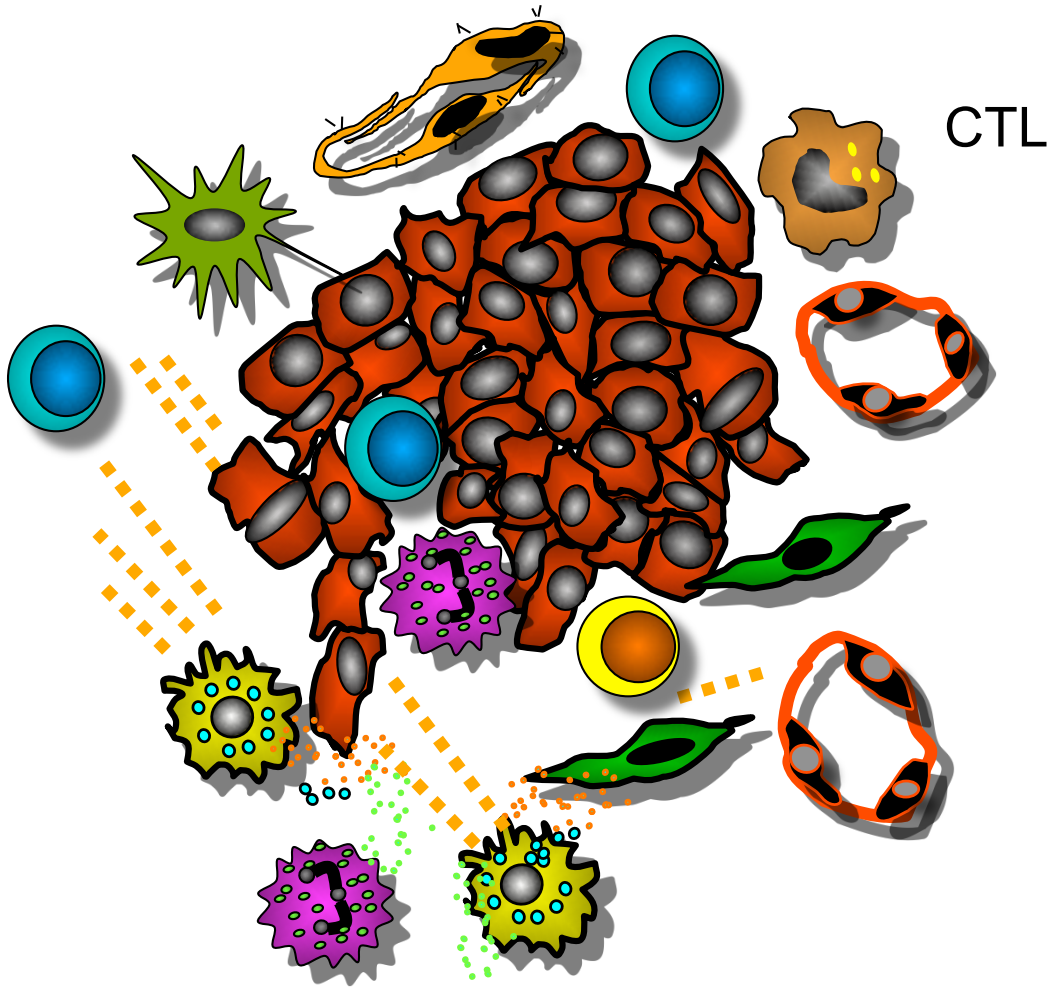
Tregs

Endothelial cells

CAFs

Cytokines…

Hypoxia..



The condition in an immunogenic (“hot”) tumor is equivalent to chronic inflammation

The immune response is silenced to avert self-damage

The key bottlenecks in raising a CTL response against cancer

1. Central tolerance

There should be tumor-specific T cells in the peripheral repertoire.
The tumor must offer recognizable (non-self) antigens.

2. Tumor-associated immunosuppression

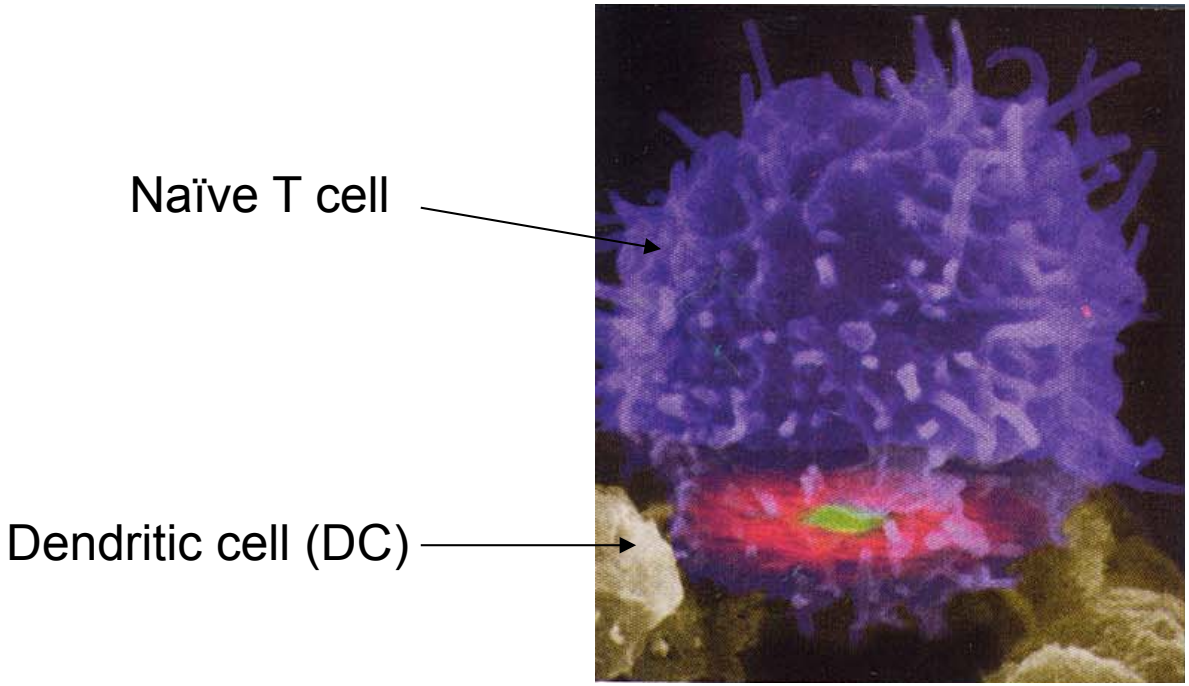
CTLs are suppressed in the tumor-microenvironment.

3. Peripheral tolerance

To kickstart and (most likely) to perpetuate the T cell response,
the tumor must activate dendritic cells.

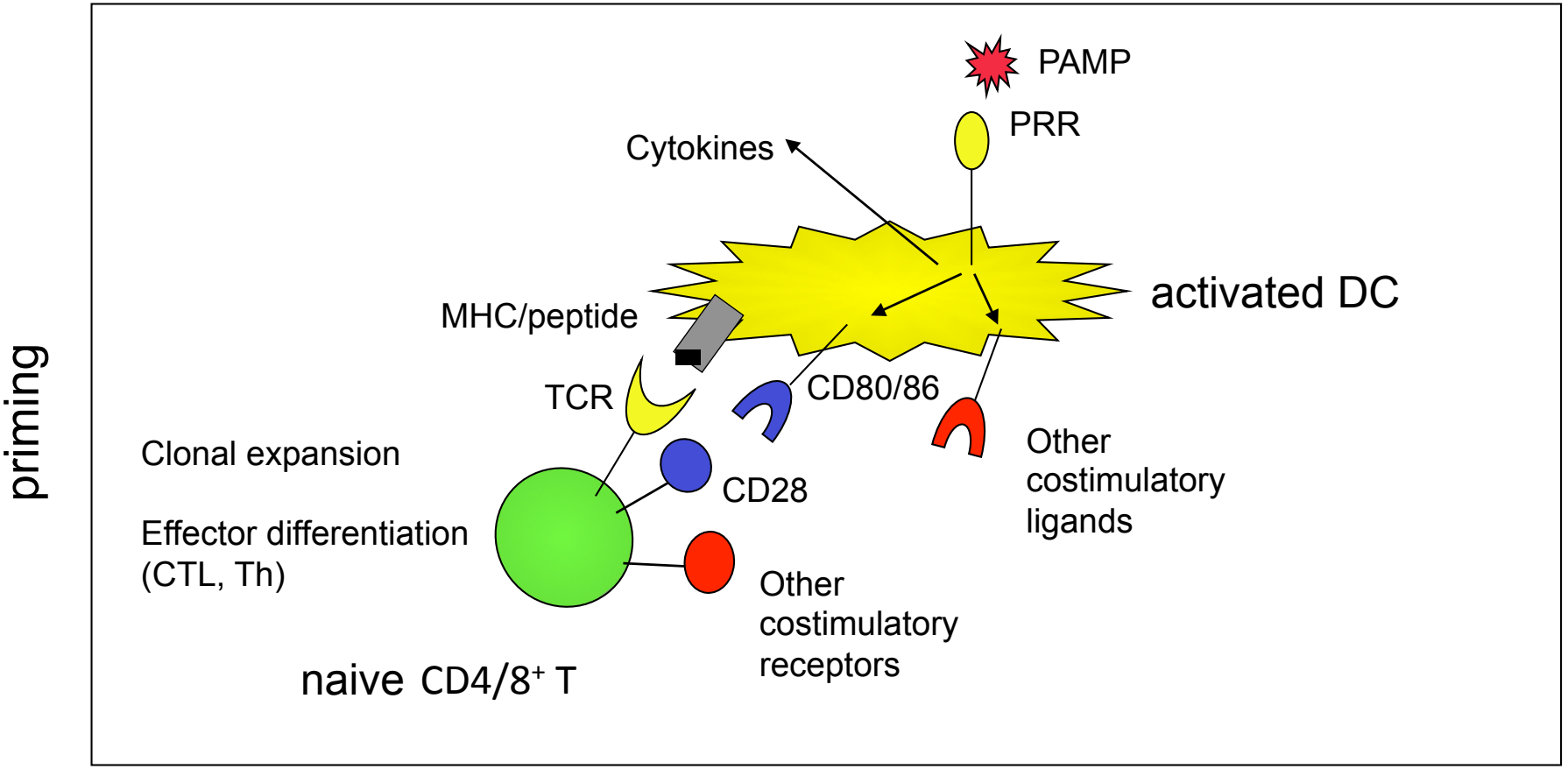
This usually does not happen.

The status of the dendritic cell dictates whether the T cell response is initiated



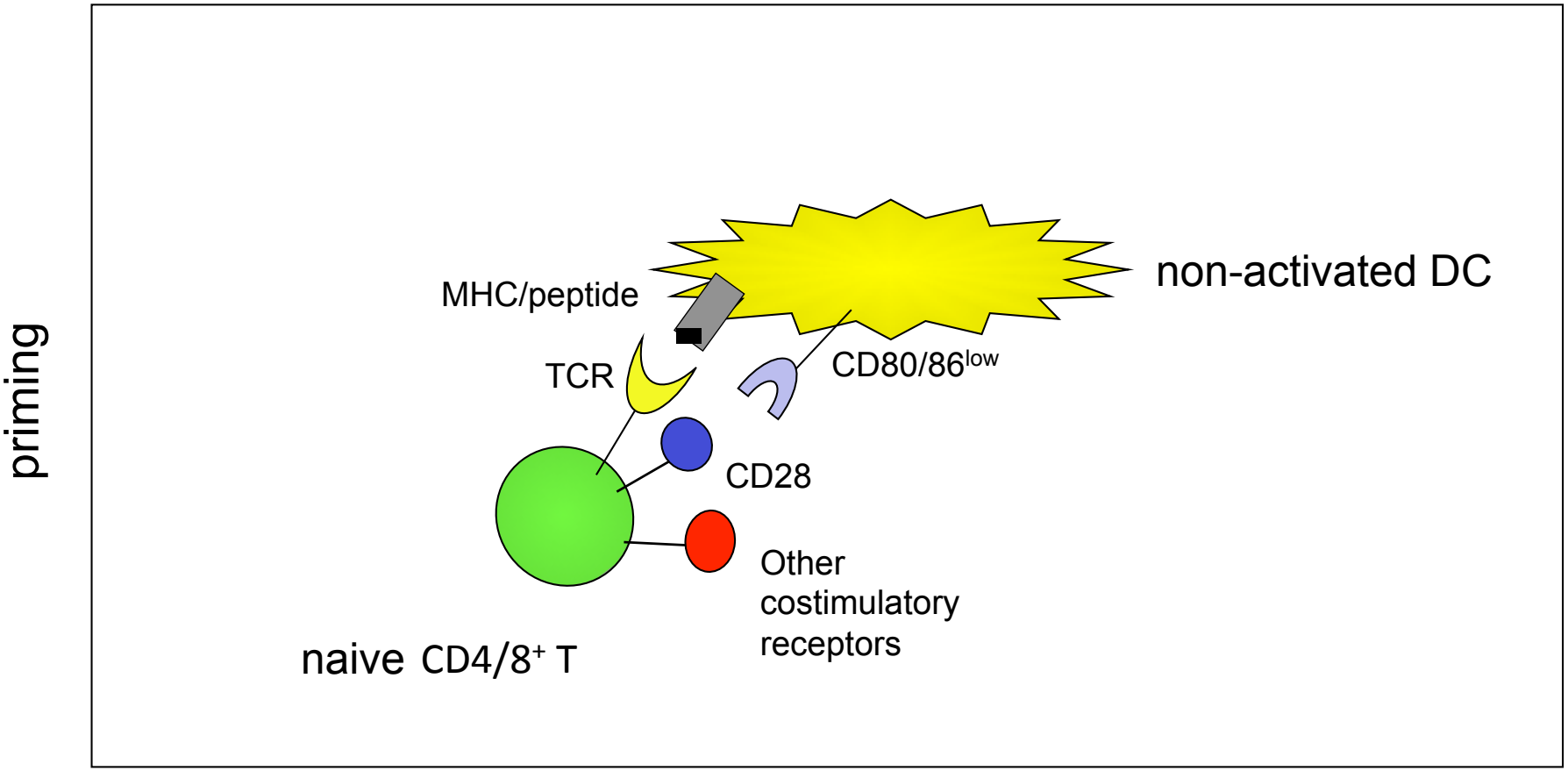
Steady state (immature) DC:	self-tolerance
Activated (mature) DC:	immunity to non-self

DC activation is required to break peripheral tolerance



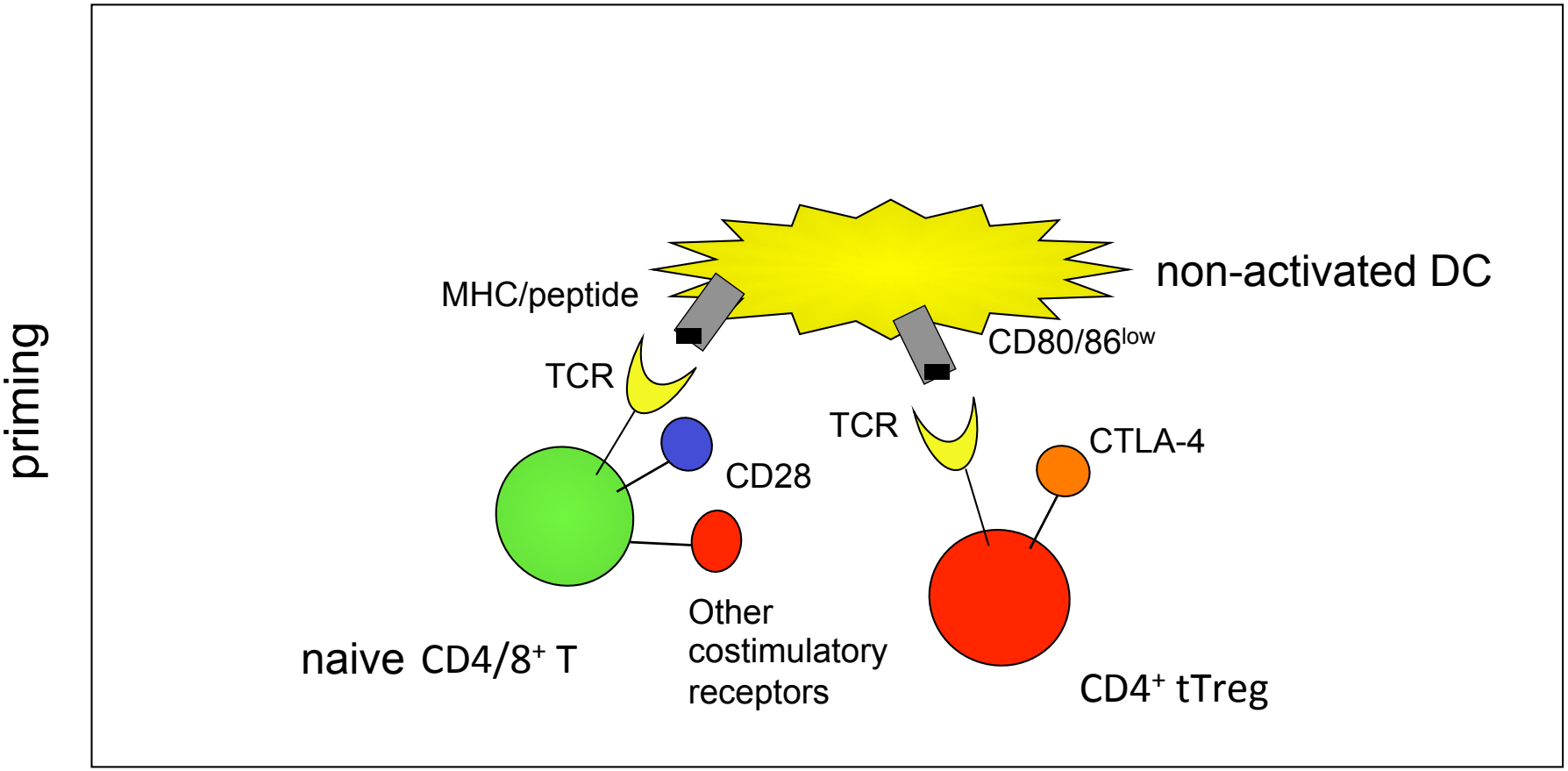
Pathogens express PAMPs

Lack of DC activation as limitation for T-cell reactivity



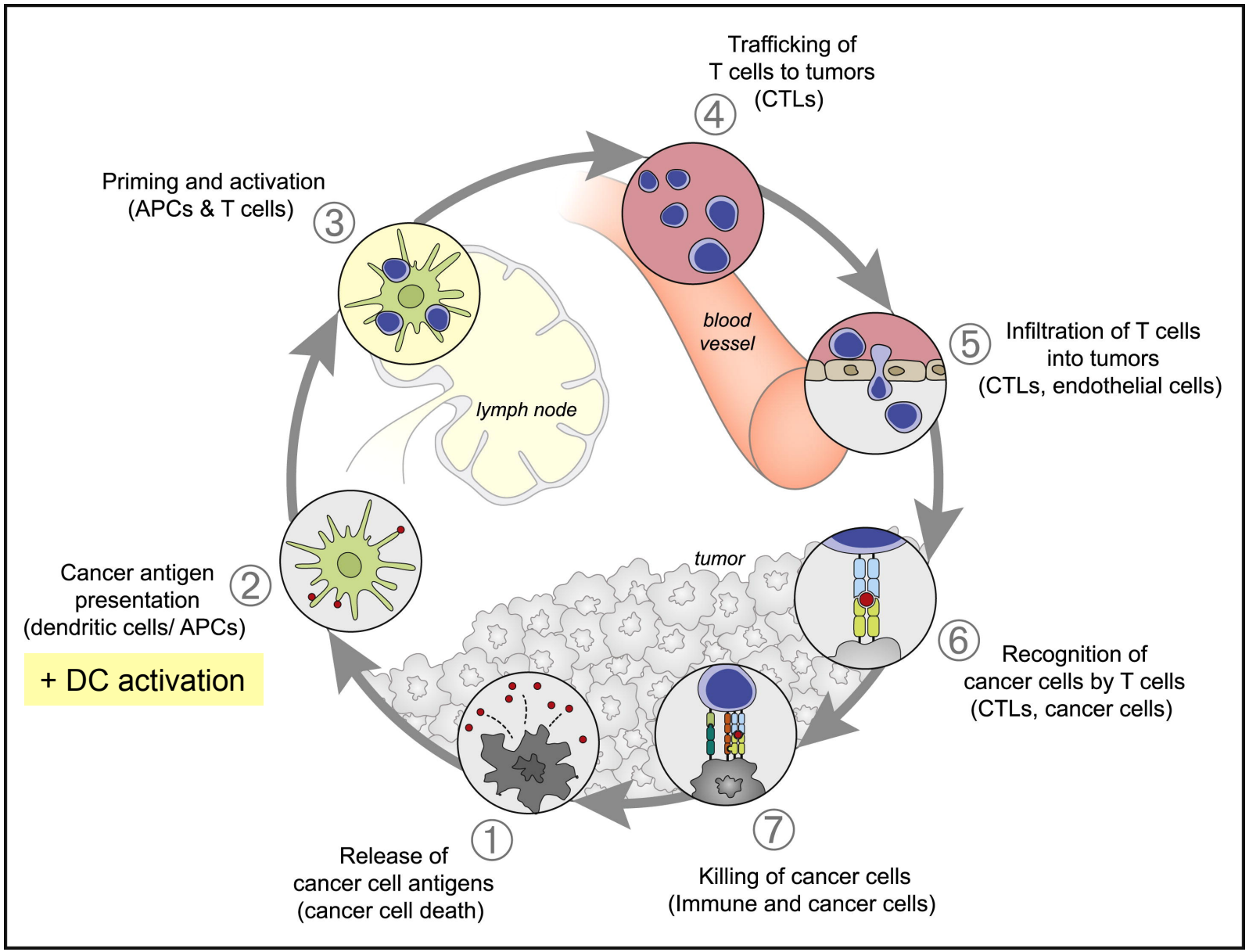
Tumor cells generally do not express PAMPs

Lack of DC activation as limitation for T-cell reactivity



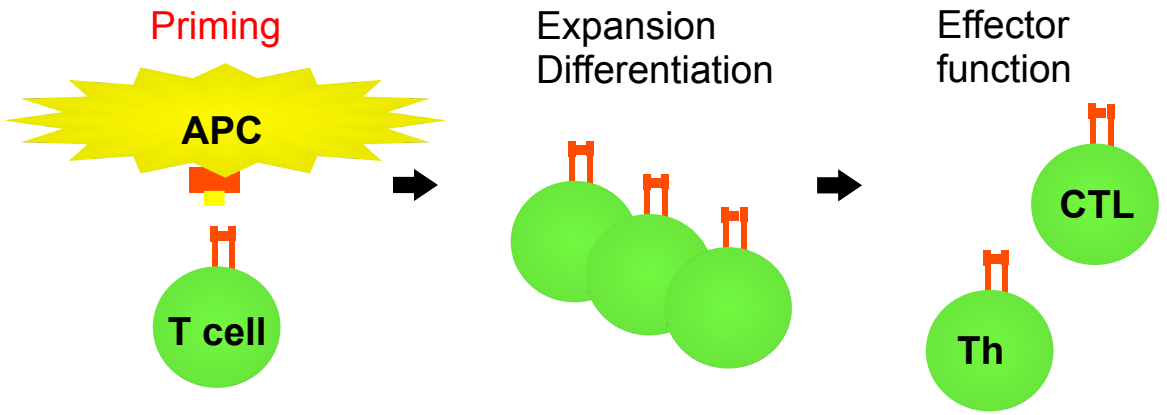
Tumor cells generally do not express PAMPs

The Cancer-Immunity Cycle



Daniel S. Chen, Ira Mellman *Immunity* 39, 1-10, 2013

So, what can you do to promote a tumor-specific T cell response?



1. Use antibodies to stimulate the T cell response

2. Vaccinate or use tumor destruction as a mode of vaccination

3. Do both 1. and 2.

4. Expand and reinfuse tumor-specific T cells taken from the tumor (TIL therapy)

5. Engineer the patient's T cells to recognize the tumor (CAR and TCR gene therapy)