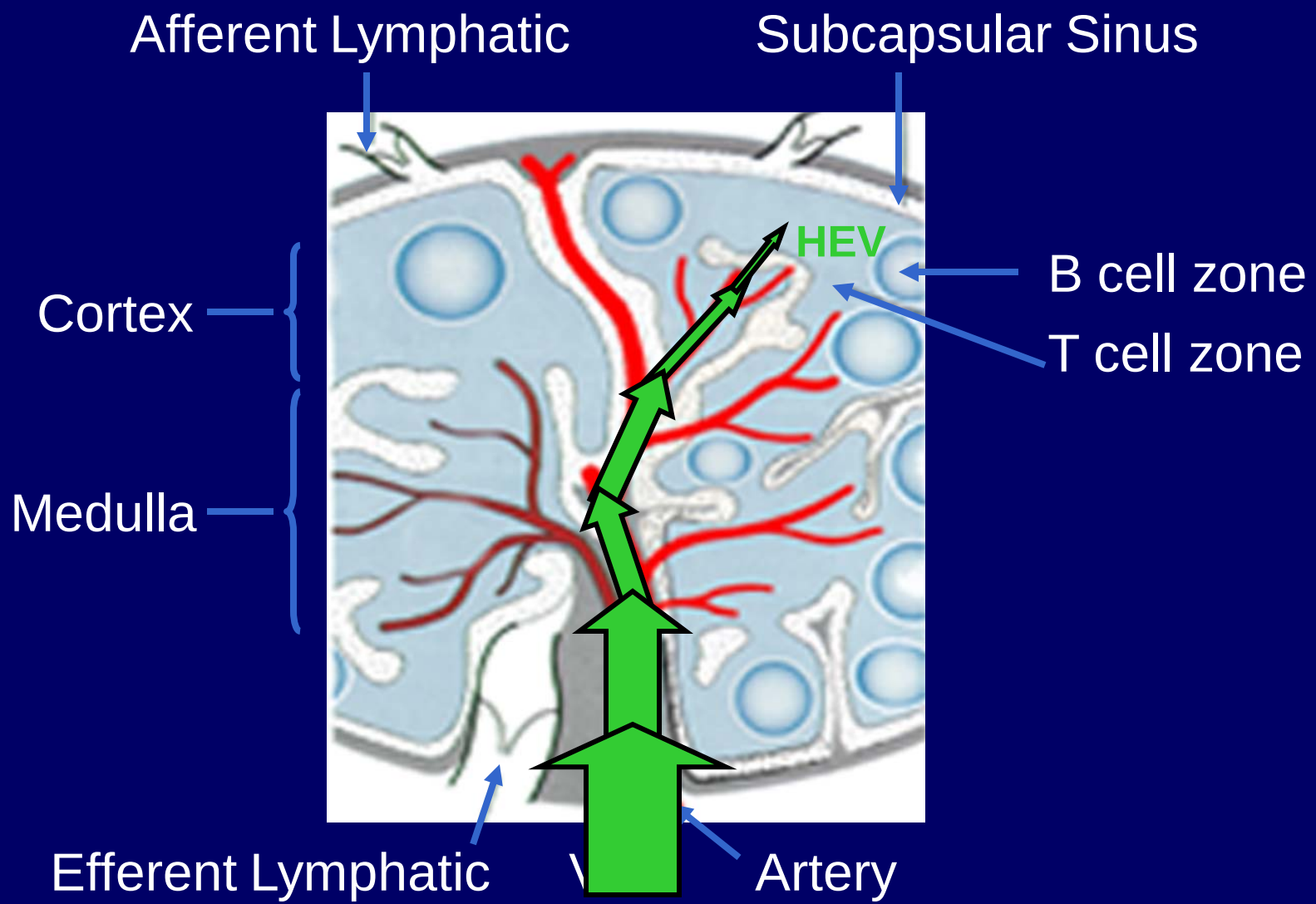
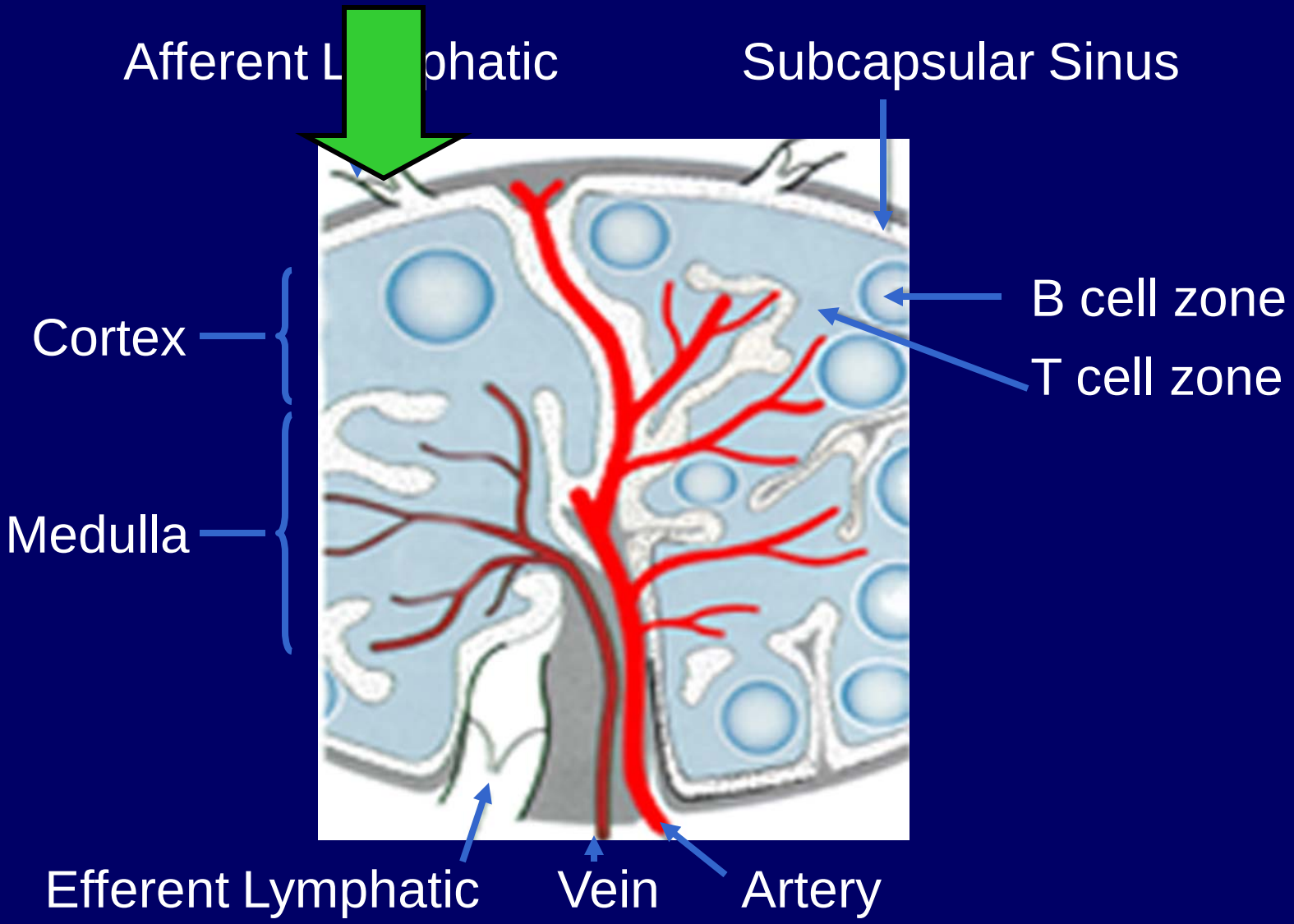
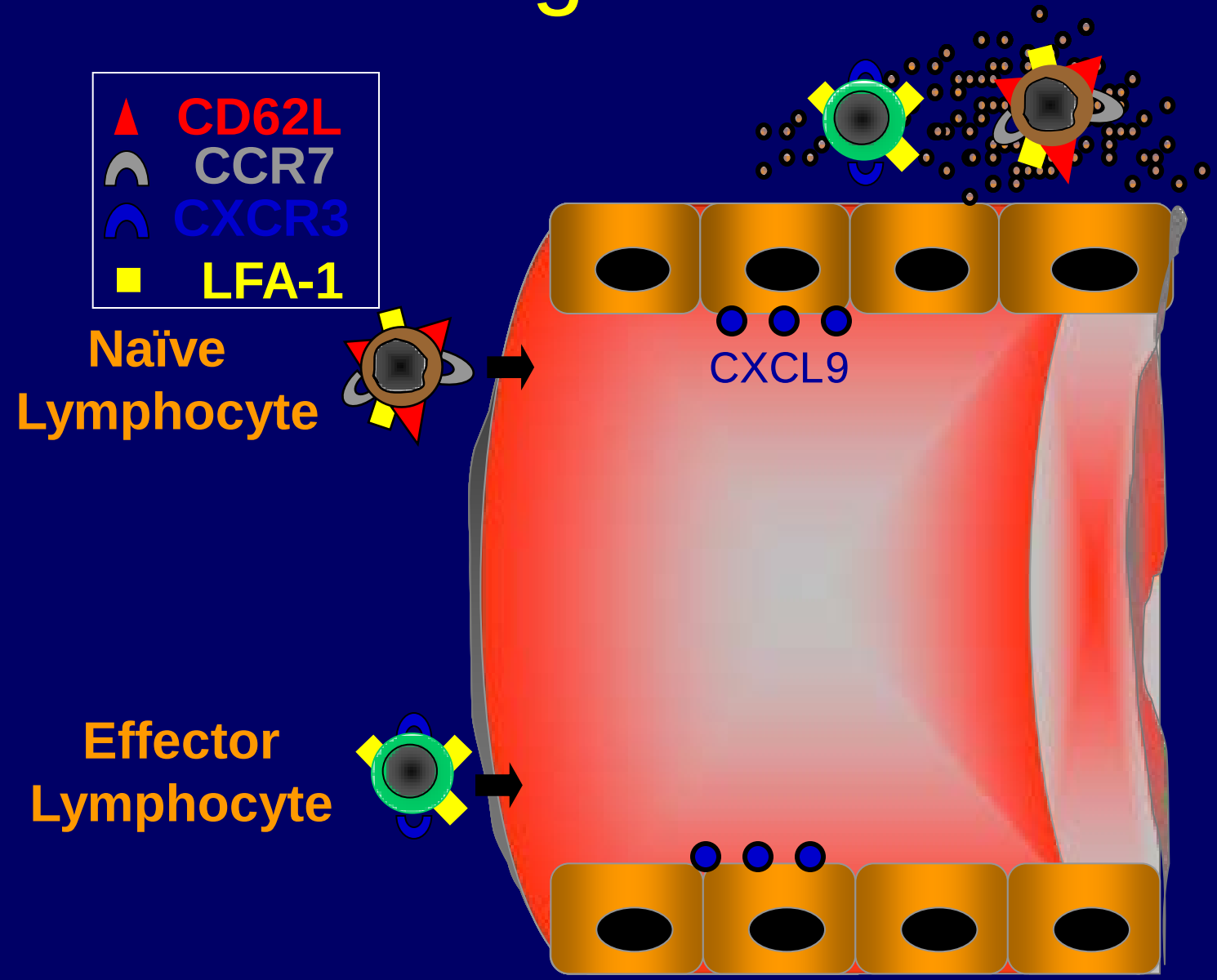
Lymphocytes enter PLN via blood



Antigens enter PLN via lymph

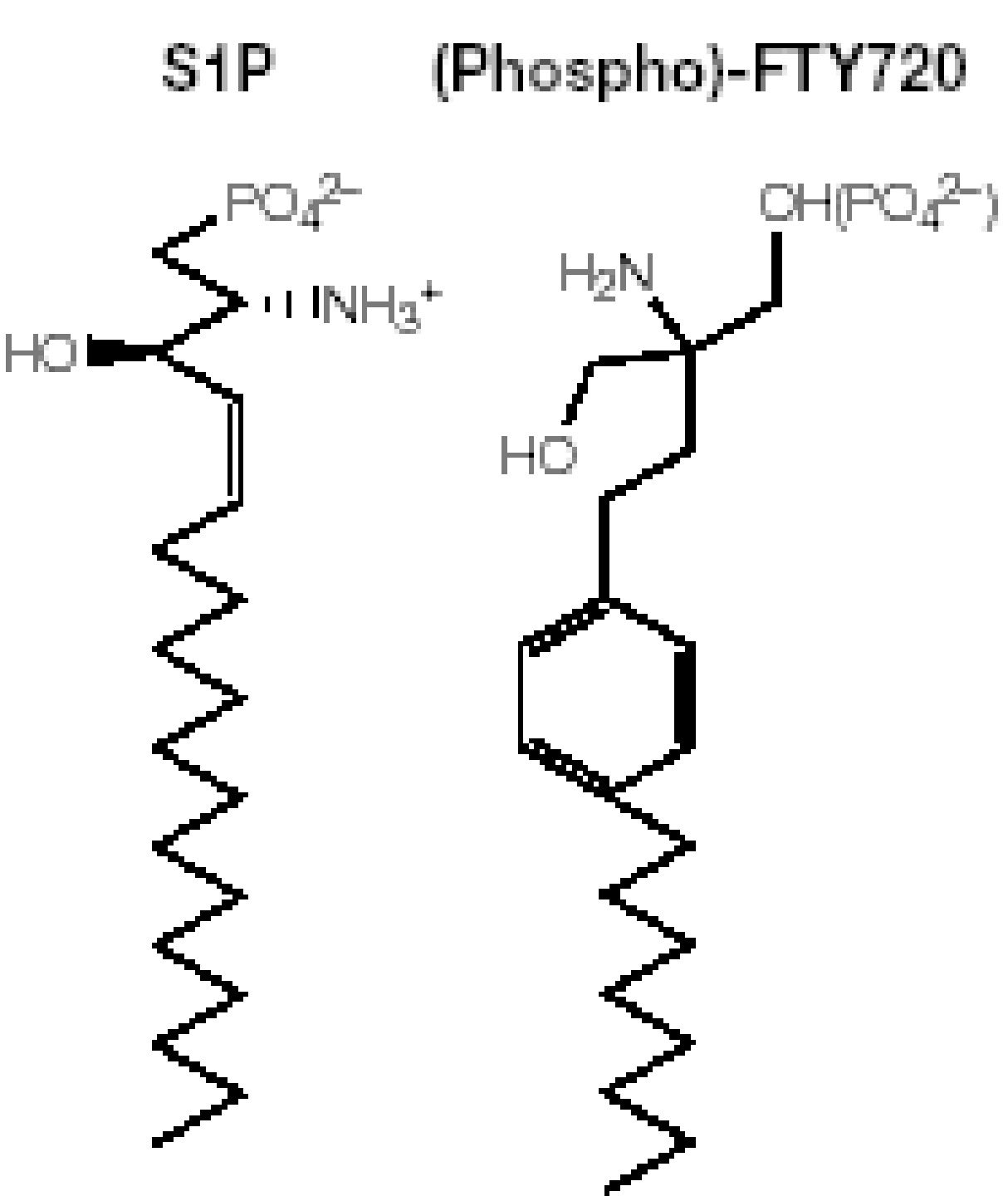


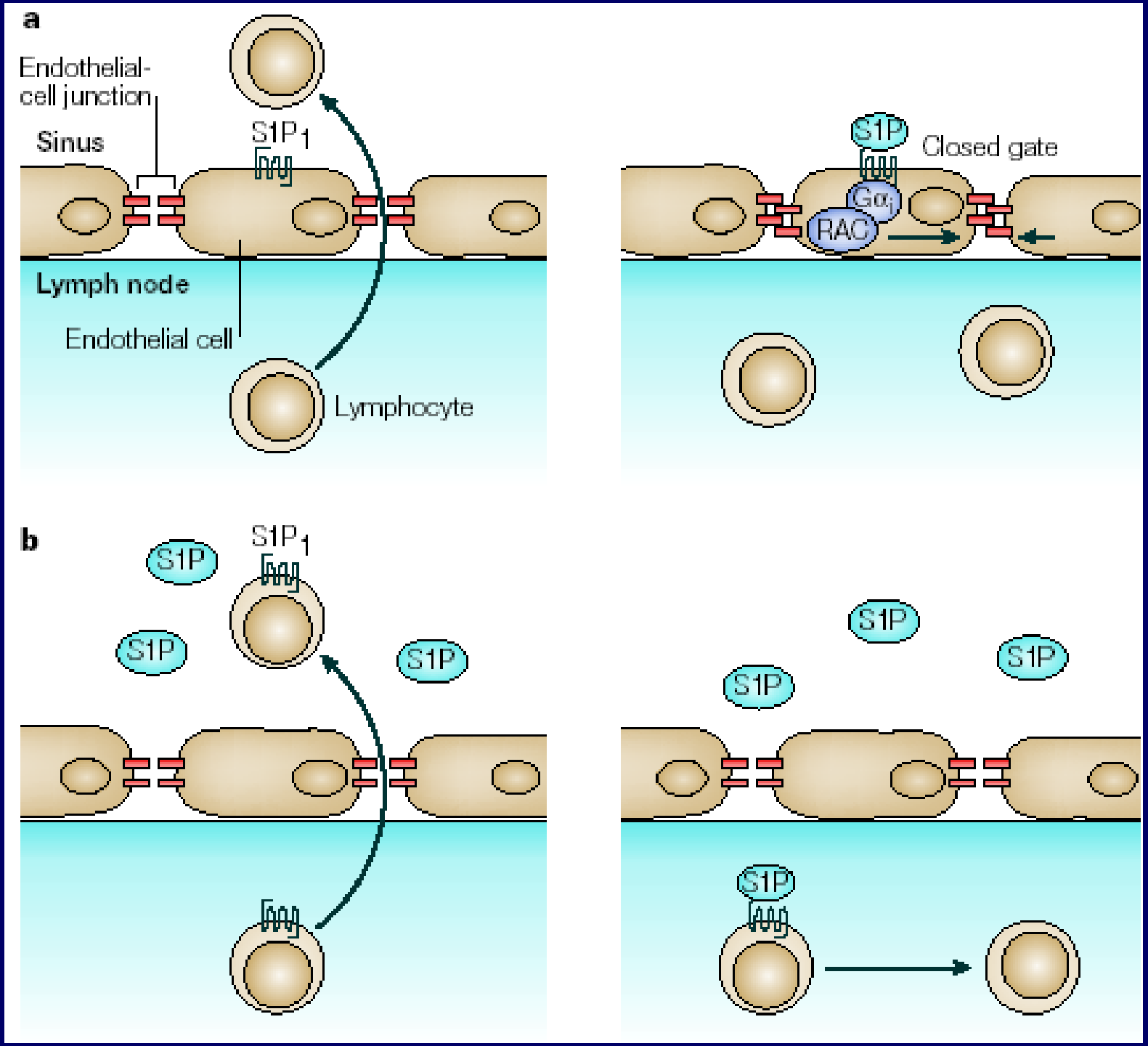
Homing to reactive PLN



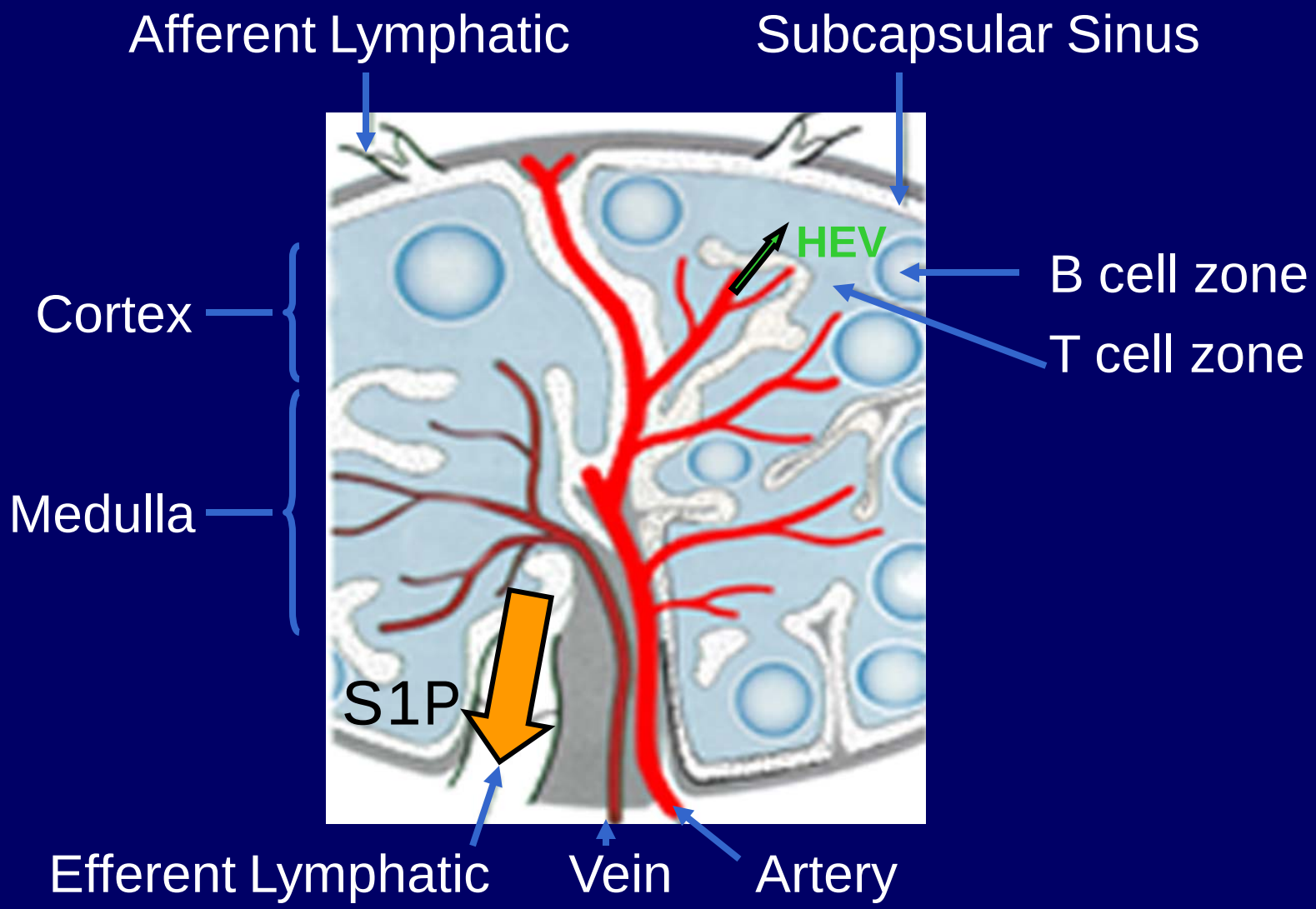
Lymphocyte sequestration in lymphoid organs

S1P
Sphingosine
1-Phosphate

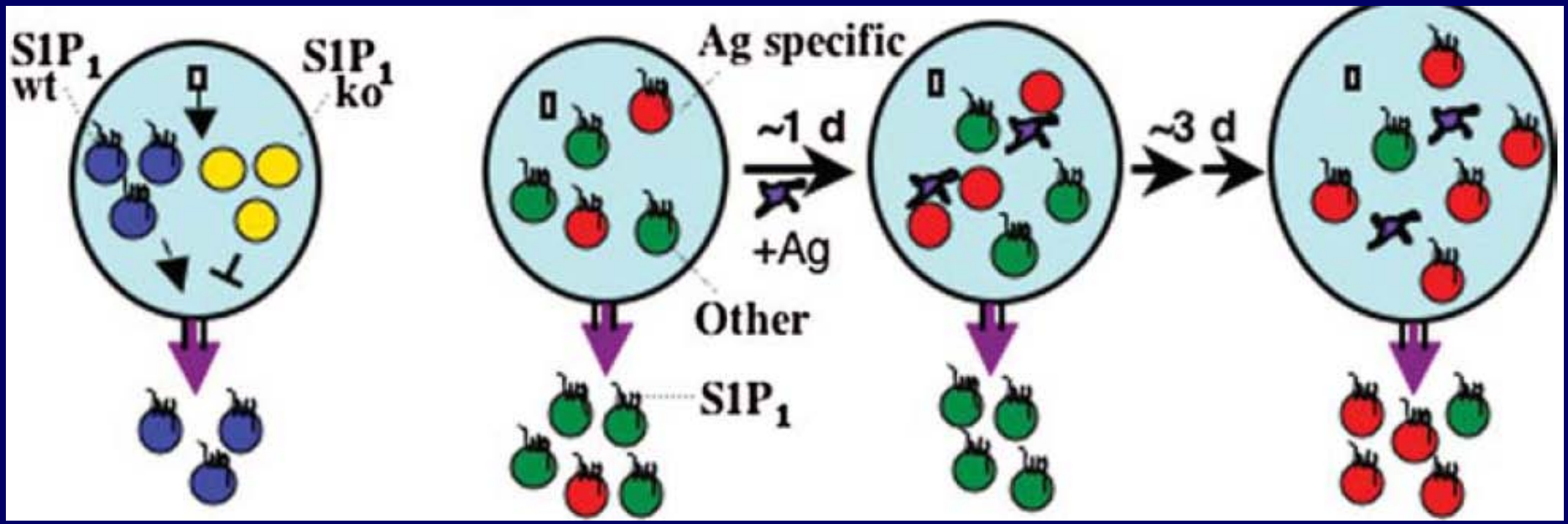



a
Endothelial-cell junction
Sinus
S1P1
Lymph node
Endothelial cell
Lymphocyte
S1P
Closed gate
Gαi
RAC
b
S1P1
S1P
S1P
S1P
S1P
S1P
S1P

Lymphocytes enter PLN via blood

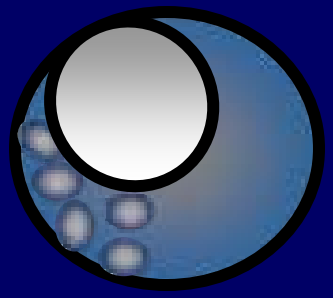


S1P1 is required for lymphocyte egress and is transiently down-regulated on activated lymphocytes

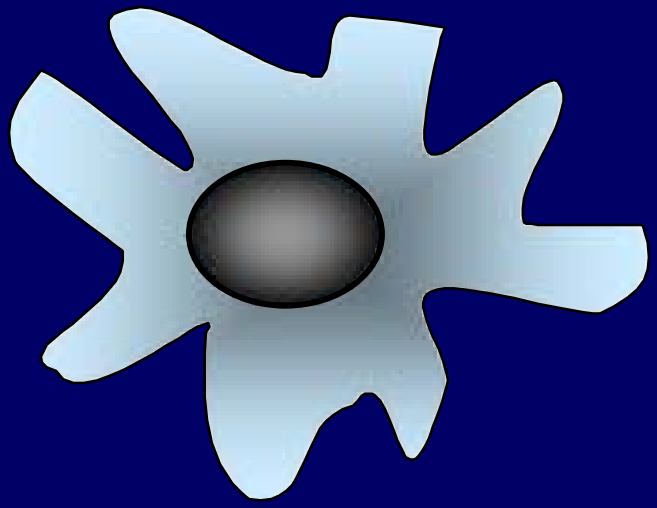


Anti-tumor immunity

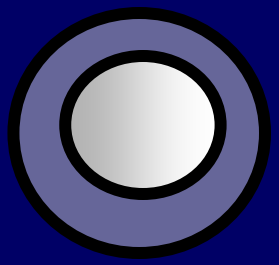
NK



APC



Lymphocyte

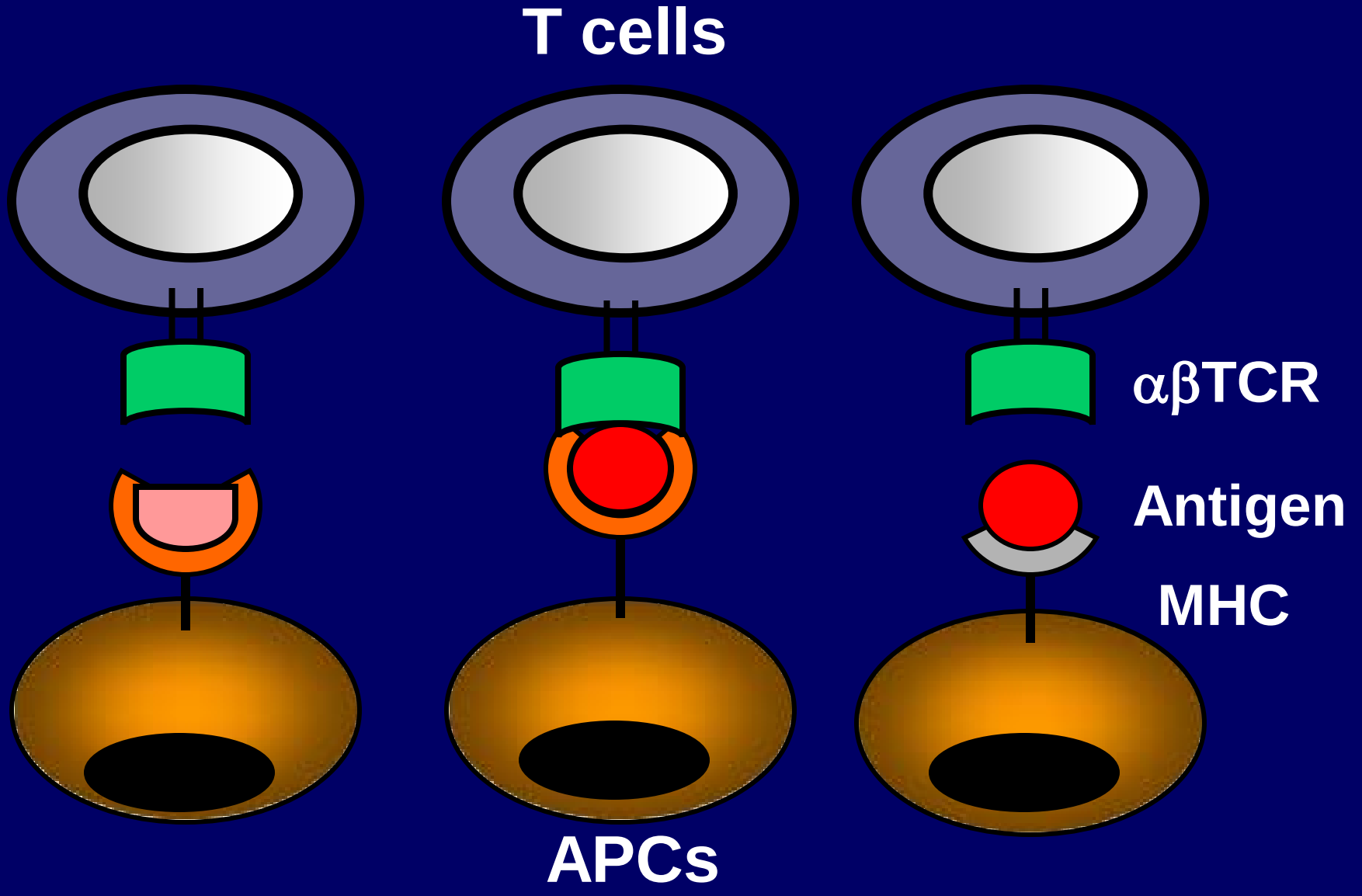


What are the antigens involved in the immune recognition of human cancers?

Proteins selectively expressed in tumors

Class of antigen	Antigen	Nature of antigen	Tumor type
Embryonic	MAGE-1 MAGE-2	Normal testicular proteins	Melanoma Breast Glioma
Abnormal posttranslational modification	MUC-1	Underglycosylated mucin	Breast Pancreas
Differentiation	Tyrosinase, Surface Ig	Melanin synthesis, Specific Ab in B-cell clone	Melanoma, Lymphoma
Mutated oncogene or tumor suppressor	Cdk4, β-catenin, Caspase-8	Cell-cycle, Signal transduction, apoptosis	Melanoma, Melanoma, Sq. c. carcinoma
Oncoviral protein	HPV type 16 E6, E7	Viral transforming gene products	Cervical carcinoma

MHC restriction

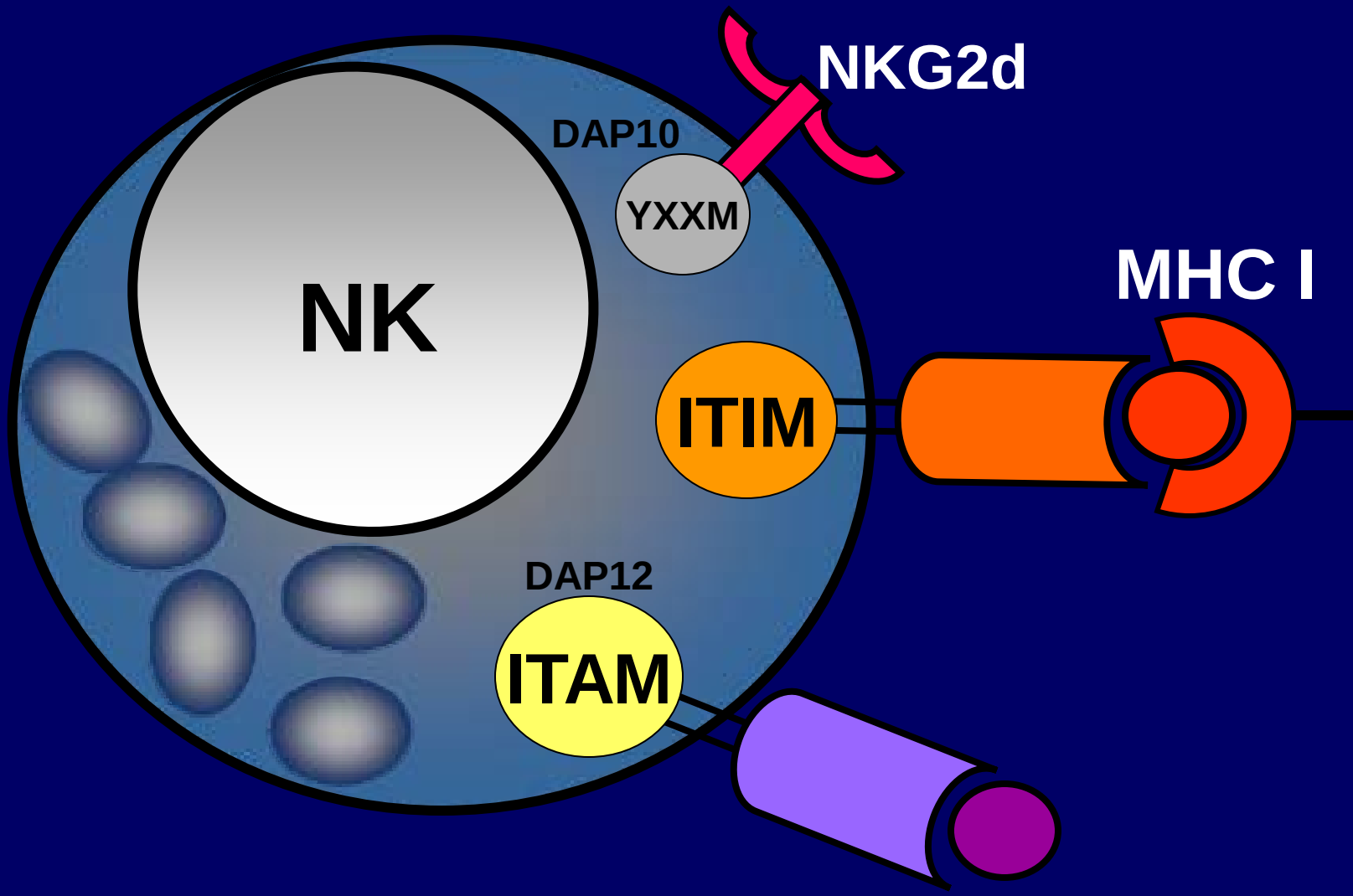


NK cells

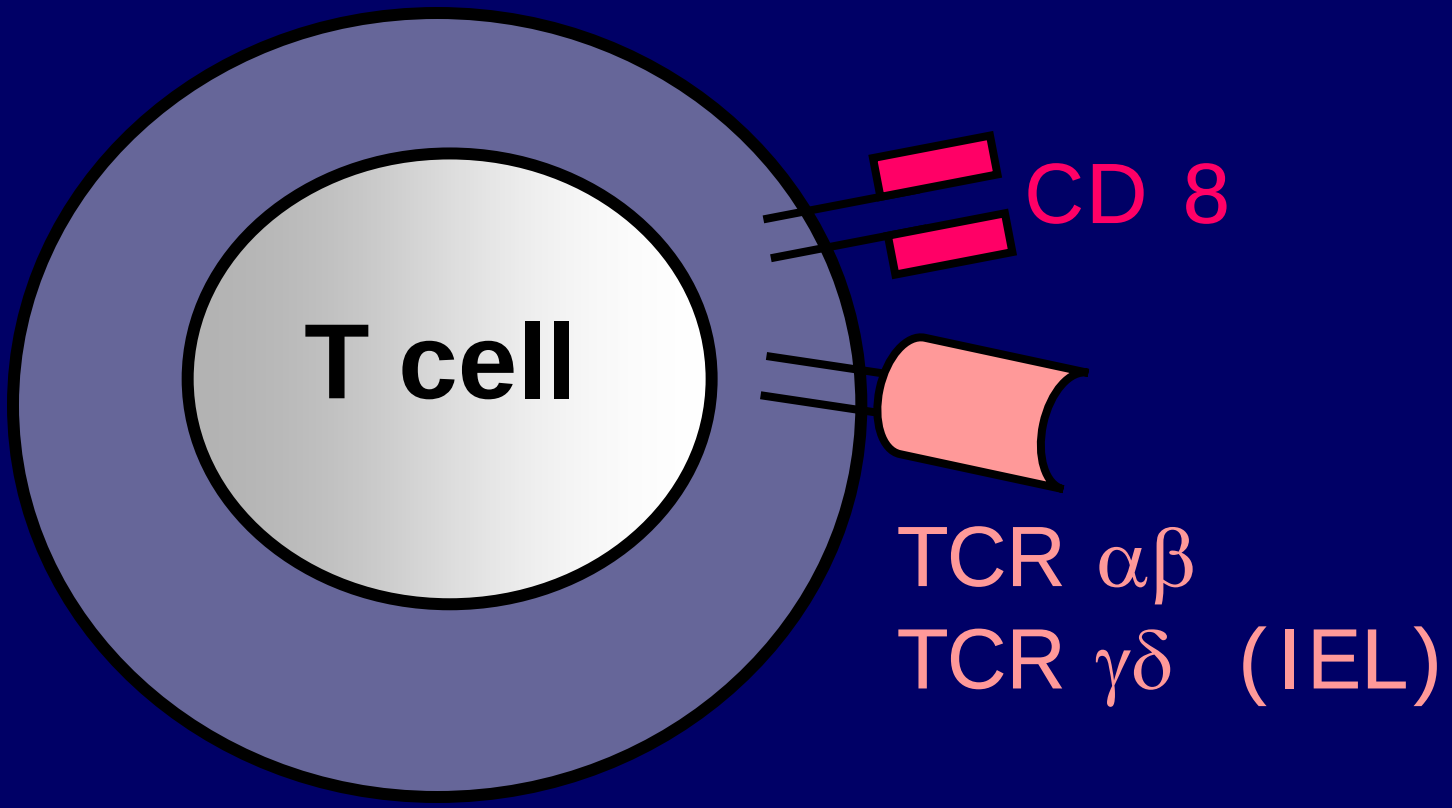
- Large, usually granular, non-T, non-B lymphocytes
- Bear no known Ag-specific receptors and are capable of killing target cells without prior immunization
- Their cytotoxic effects are not MHC restricted

ITIM = immunoreceptor tyrosine-based inhibitory motif

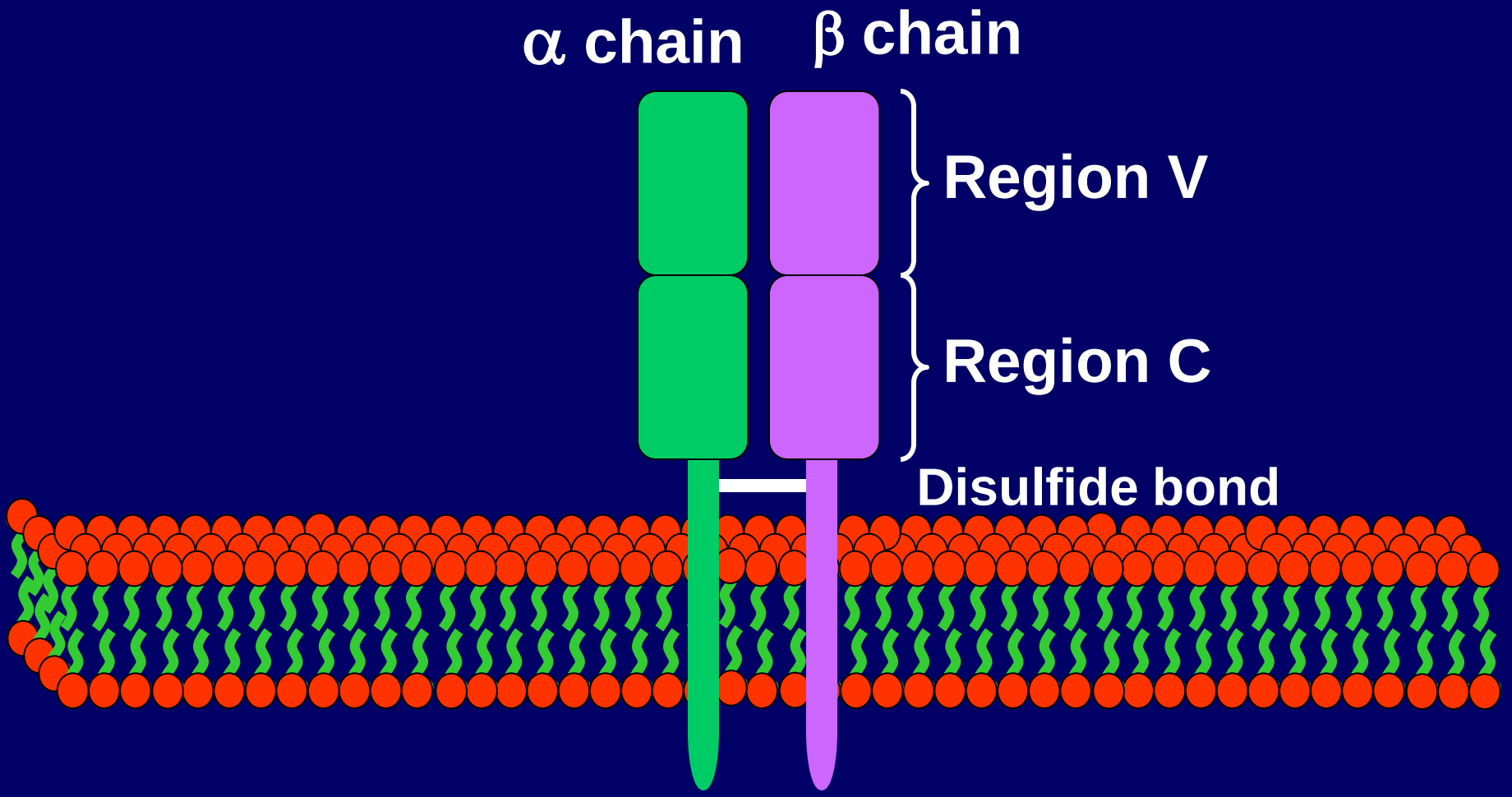
ITAM=immunoreceptor tyrosine-based activating motif



T cells



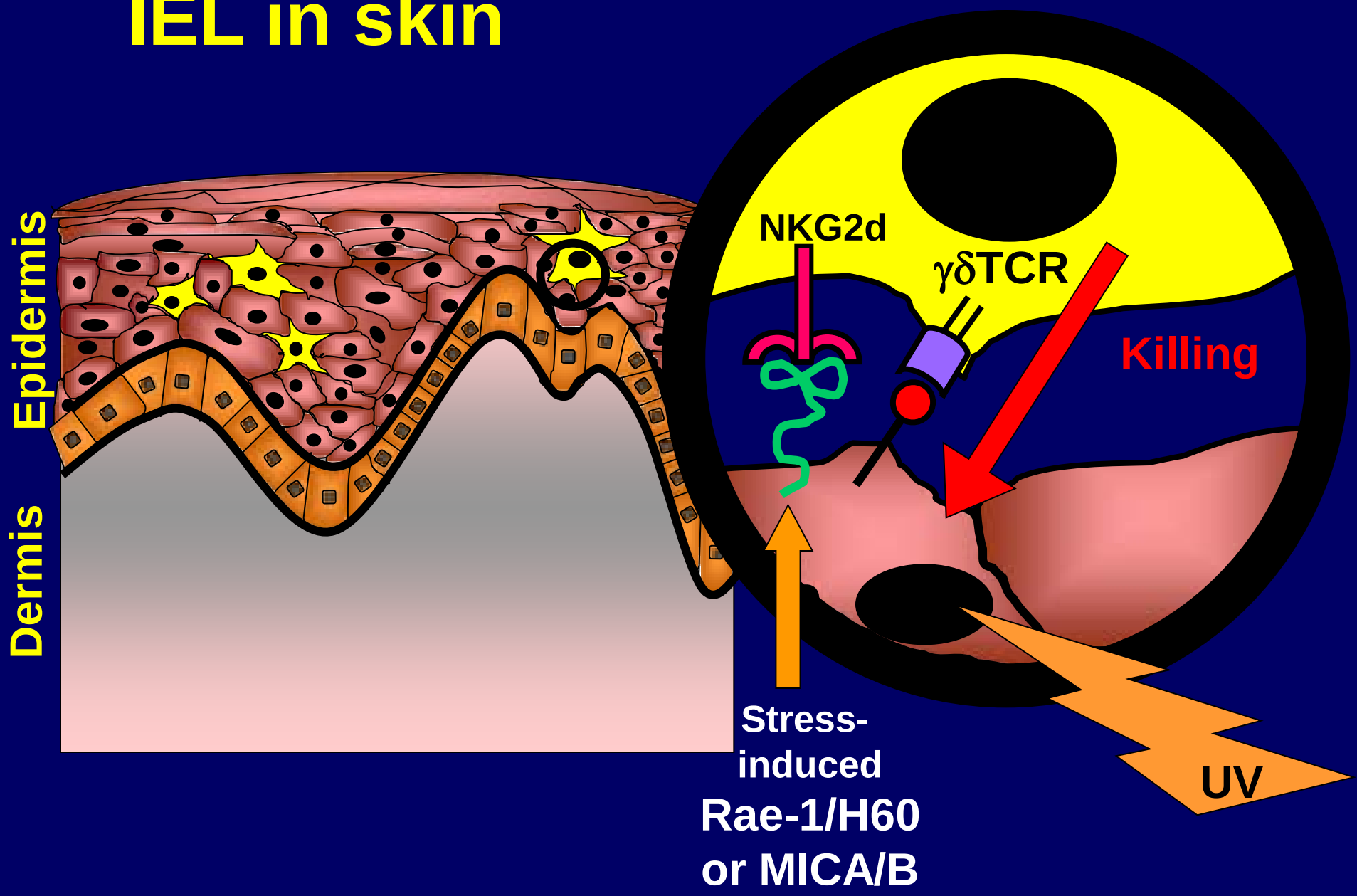
T cell receptor (TCR)



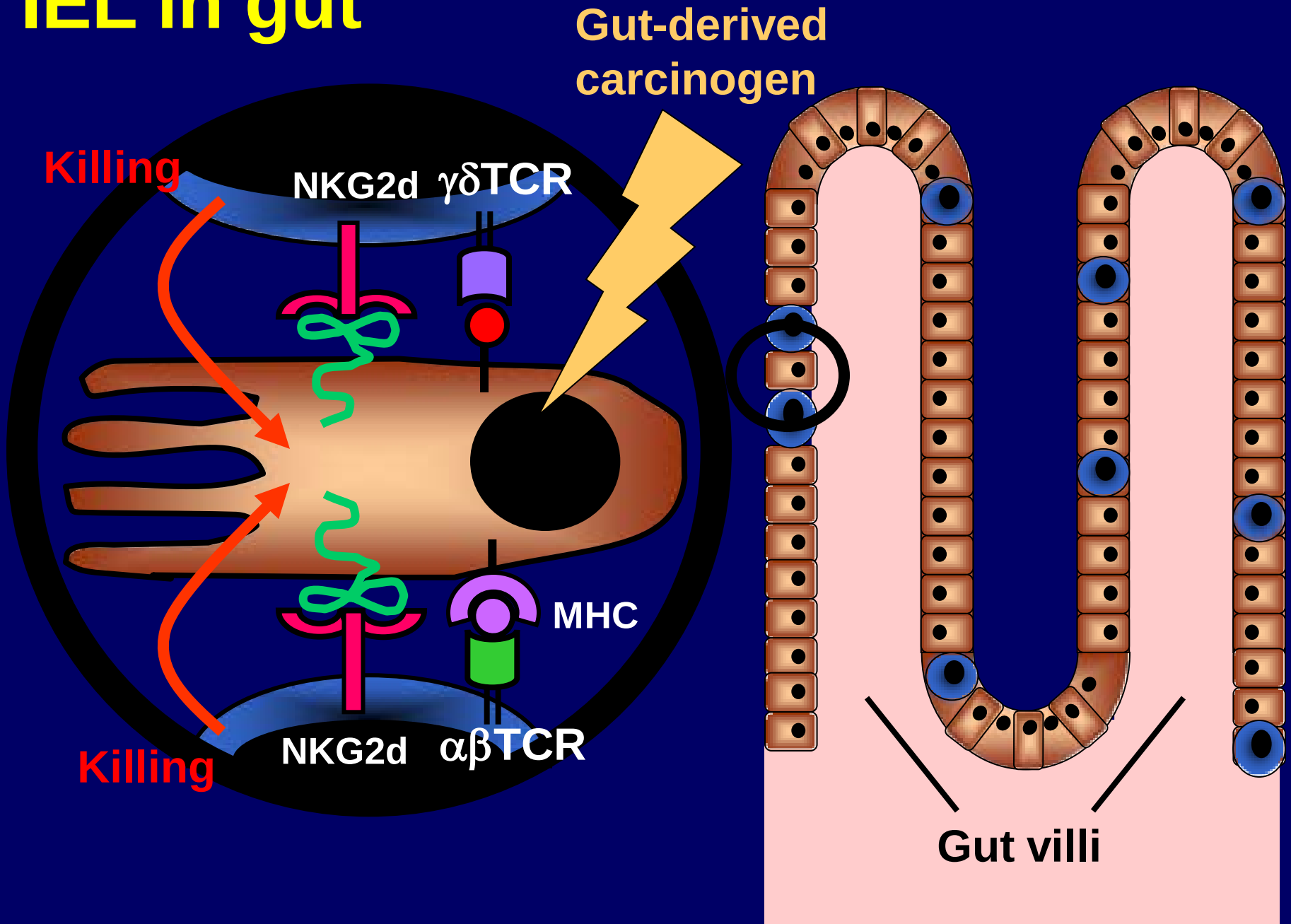
IEF (Intraepithelial lymphocytes)

- Lymphocytes populating epithelial tissues, including epidermis, small intestine and reproductive tract
- Bear an alternative form of T cell receptor with γ and δ chains. These receptors are characterized by very limited diversity
- Unlike $\alpha\beta$ T cells, $\gamma\delta$ T cells do not generally recognize Ag as peptides presented by MHC molecules

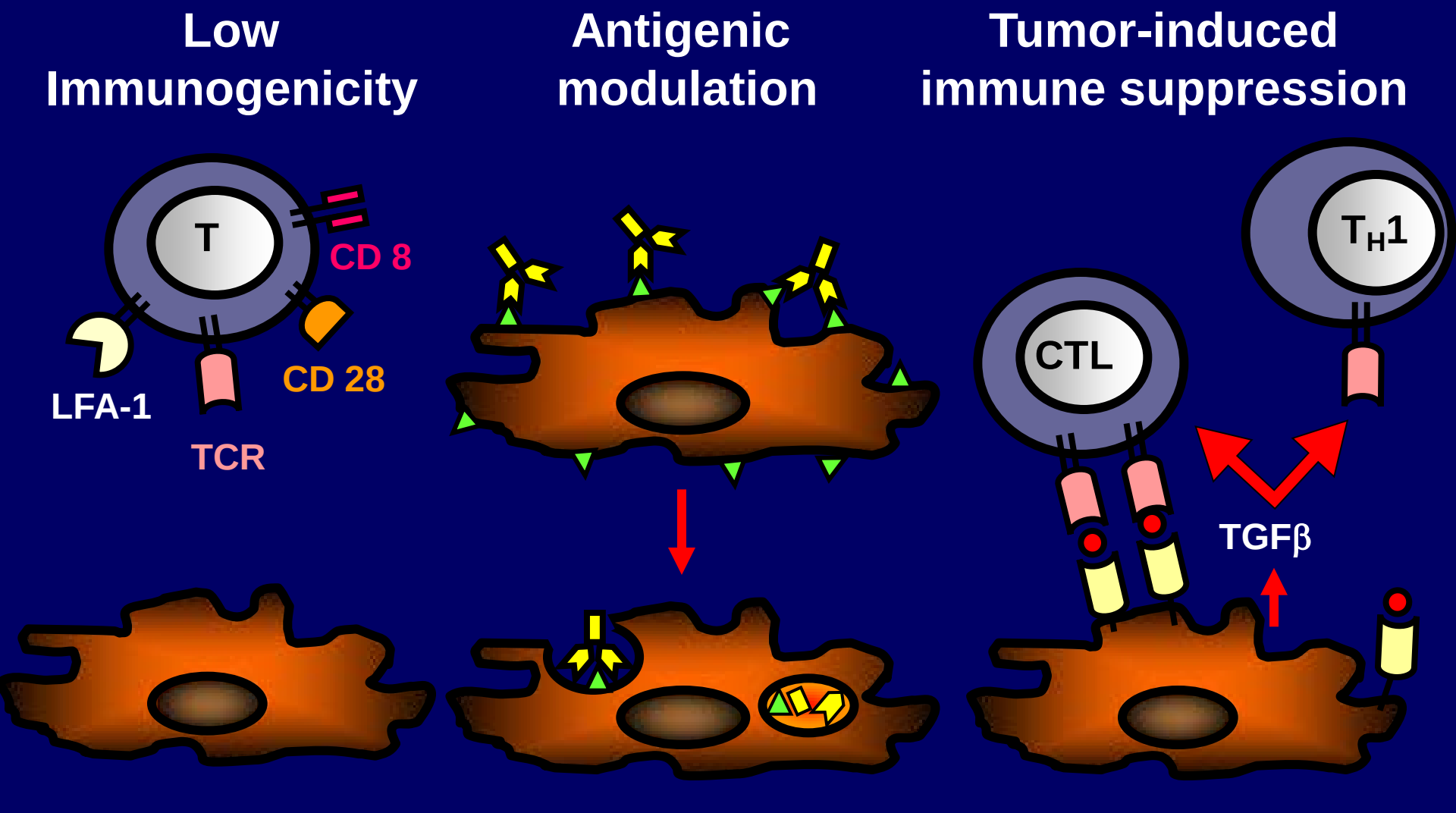
IEL in skin

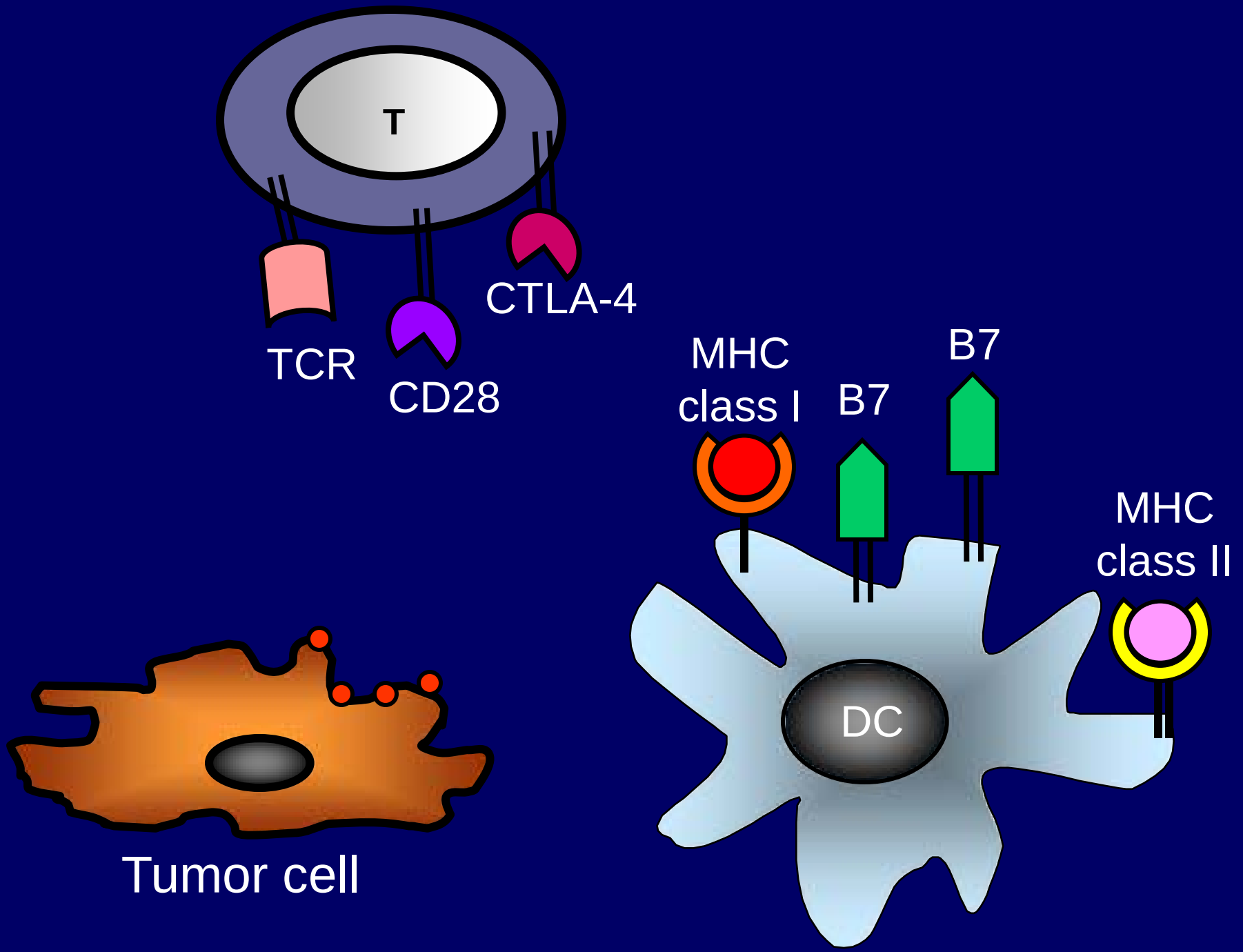

Epidermis
Dermis
NKG2d
γδTCR
Killing
Stress-
induced
Rae-1/H60
or MICA/B
UV

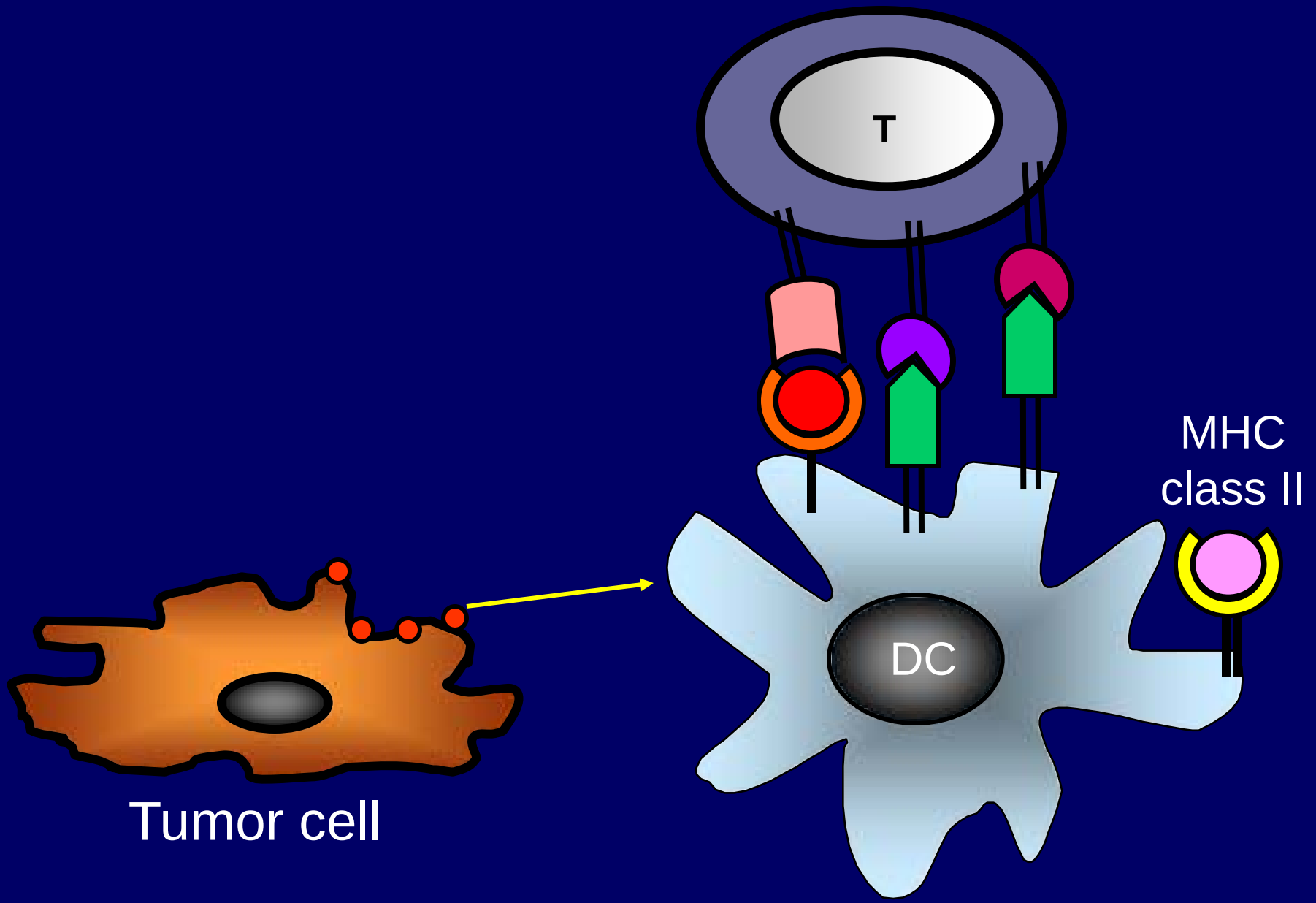
IEL in gut


Gut-derived carcinogen
Killing
NKG2d
γδTCR
MHC
Killing
NKG2d
αβTCR
Gut villi

Mechanisms whereby tumors escape immune recognition




T
CTLA-4
TCR
CD28
MHC
class I
B7
B7
MHC
class II
DC
Tumor cell


T
MHC
class II
DC
Tumor cell

Can anti-tumor T cells be generated in patients by immunization with cancer antigens?

Vaccine approaches to cancer treatment

- Vaccines based on cancer cells
- Whole cancer cells (both autologus or allogenic preparations)
- Gene-modified cancer cells (genes encoding cytokines or co-stimulatory molecules)
- Cancer cell extracts (lysates, membranes and heat-shock proteines, stress -induced proteins -MICA/B)
- Cancer cell fused to APCs

Vaccine approaches to cancer treatment

- Vaccines based on the genetic identifications of cancer Ag
- Purified cancer Ag (natural or recombinant)
- Synthetic peptides
- “Naked” DNA (plasmides)
- Recombinant viruses (adenovirus, vaccinia)
- Recombinant bacteria (Listeria)

What mechanisms limit cancer regression despite in vivo generation of anti-tumor T cells?

- Lack of stimulation of CD4 T cells
- Insufficient levels of circulating anti-tumor T cells
- T cells do not have sufficient avidity for tumor cells
- Generation of tolerant T cells

Infections agents as antigens to prevent or treat cancer

Bacteria	*Helicobacter pylori*	Gastric cancer and lymphoma
Virus	*H. papiliomavirus* *Hepatitis B and C* *HIV* *Epstein-Barr virus*	Cervical and anal cancer Liver cancer Kaposi's sarcoma Lymphomas
Parasite	*Schistosomes*	Bladder cancer