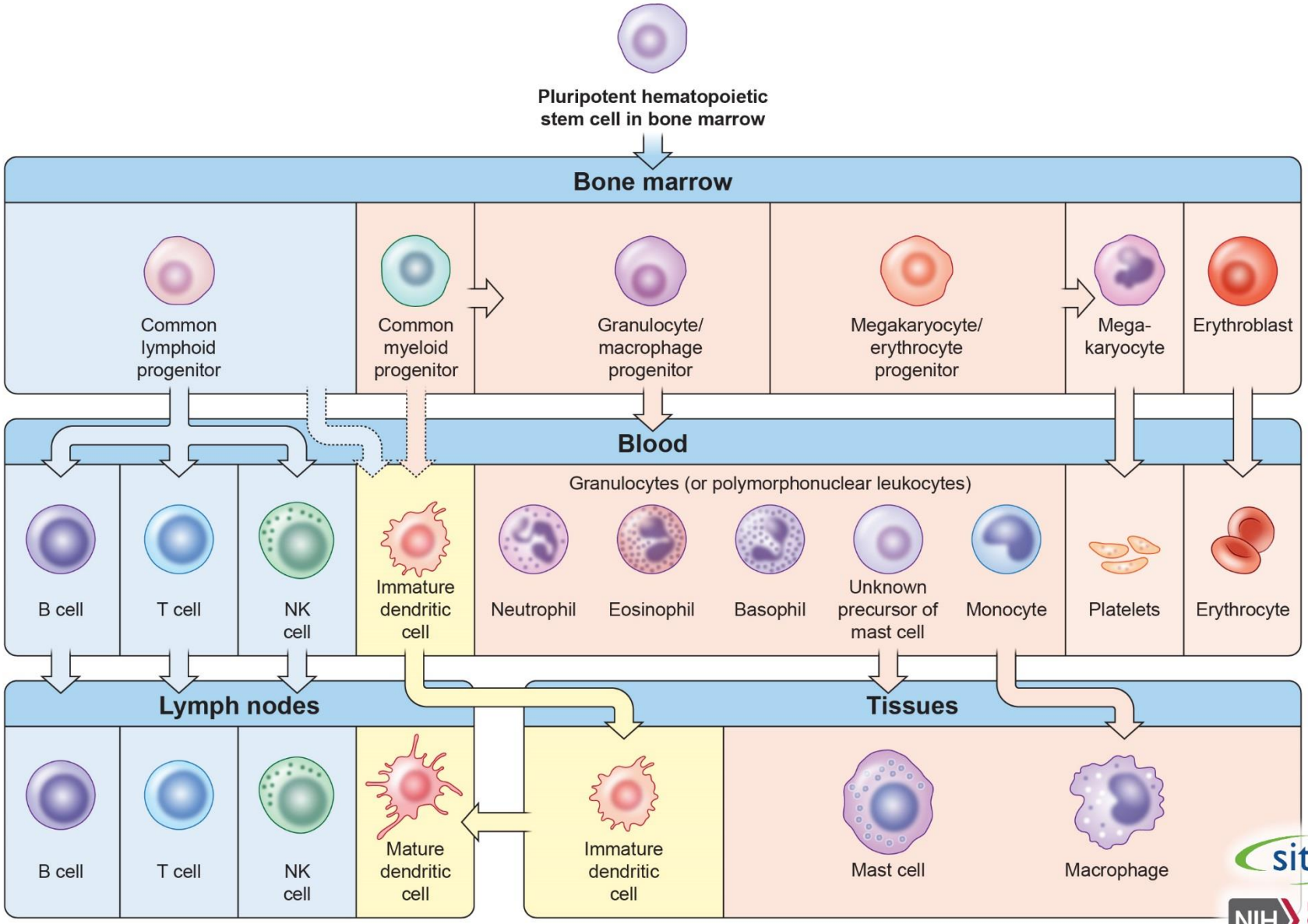
Presentation Outline

- Review of the Immune System and the Immune Response
- Nature of the Immune Response to Cancer
  - Evidence for it
  - Evidence that it matters
  - Understanding how cancer escapes the immune response

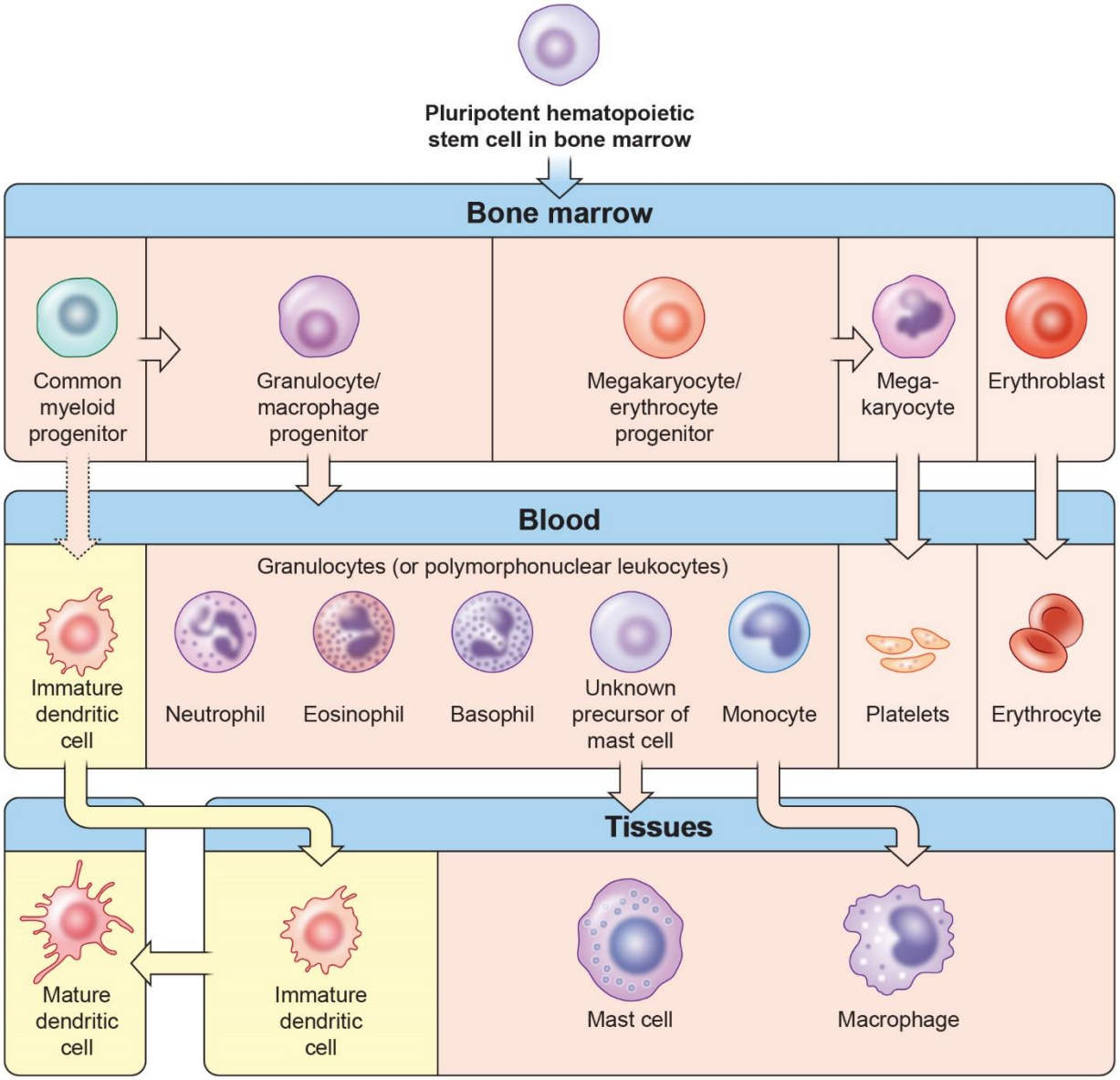
Disclosures

- Agenus, Inc.: Consulting Fees and Ownership Interest
- I will NOT be discussing non-FDA approved treatments during my presentation.

Immune cells are derived from stem cells in the bone marrow



Myeloid cells



- Derived from a common progenitor
- Comprises most of the cells of the innate immune system
- Functional maturation may happen in tissue in response to danger signals

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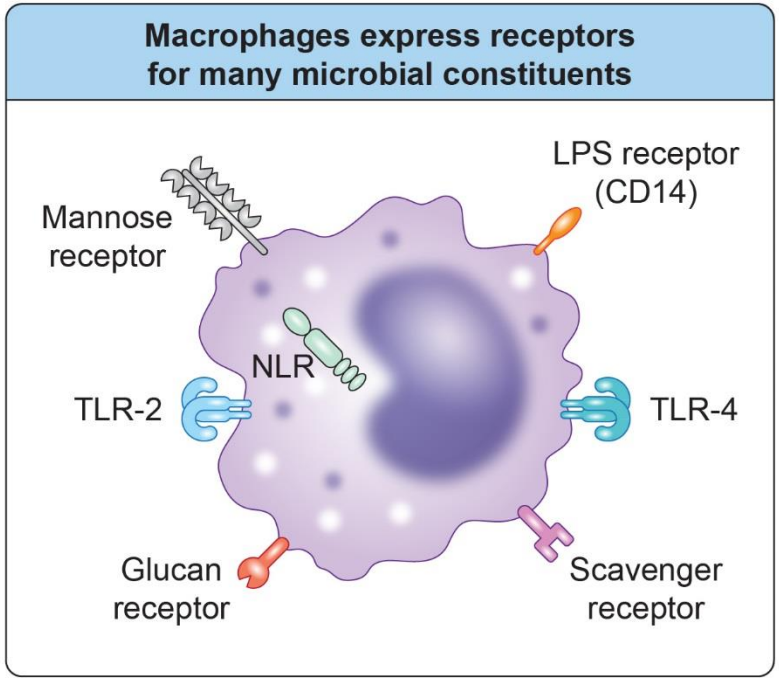
Innate responses are initiated upon recognition of "danger signals" by pattern recognition receptors (PRRs)



"Danger signals"

- Pathogen-associated molecular patterns (PAMPs)
  - Bacteria proteins
  - viral DNA/RNA
- Damage-associated molecular patterns (DAMPs)
  - Products of dying cells

Types of PRRs

- Toll-like receptors (TLR)
- C-type lectin receptors
- NOD-like receptors (NLRs)
- RIG-I-like receptors

Receptors can be on the cell surface or intracellular (NLRs)

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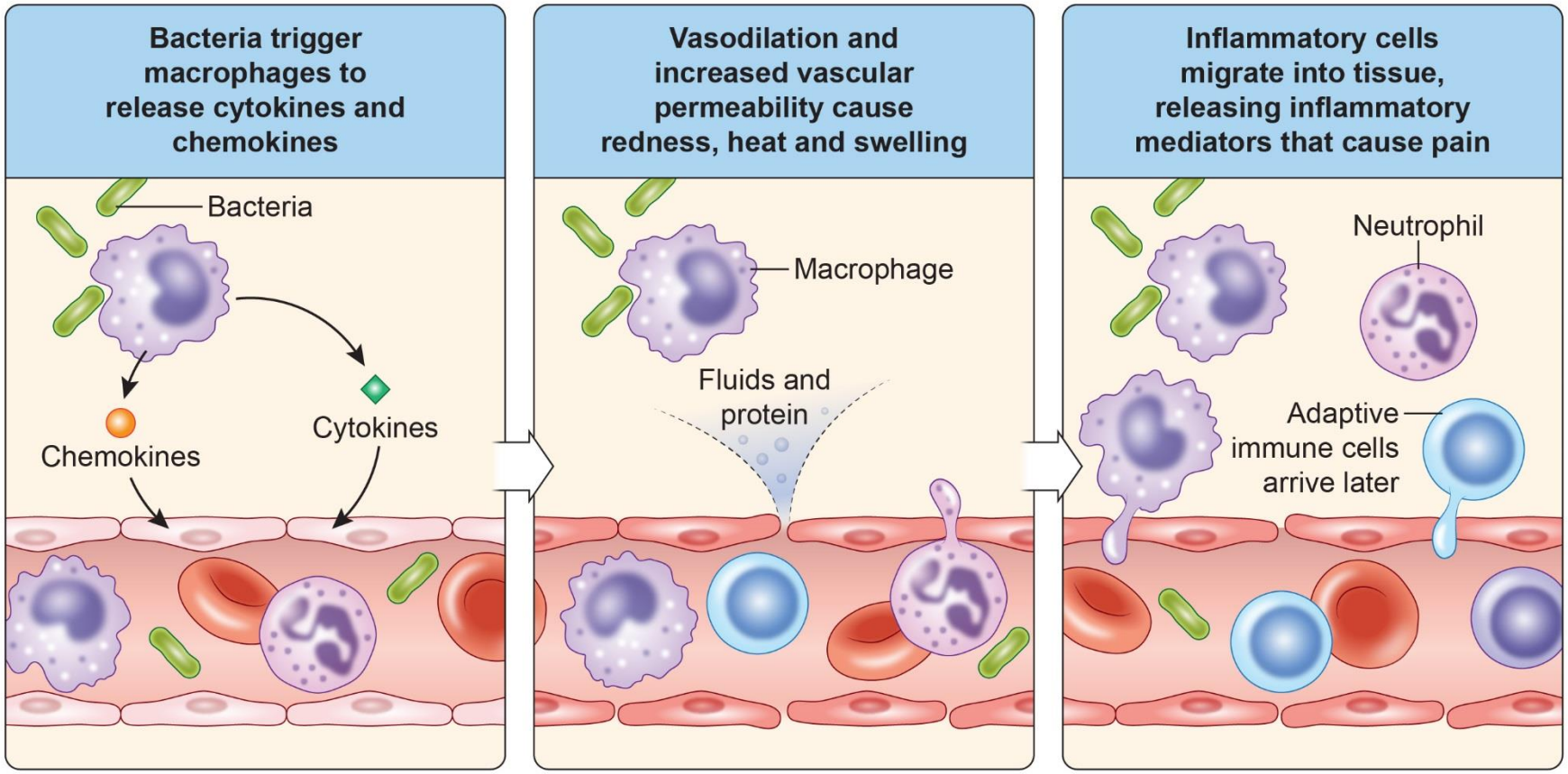
Infectious agents first activate innate immune cells resulting in an inflammatory response



Cytokines are proteins that immune cells use to communicate/regulate other immune cells, not all cytokines are inflammatory

Chemokines are a group of cytokines that attract other immune cells

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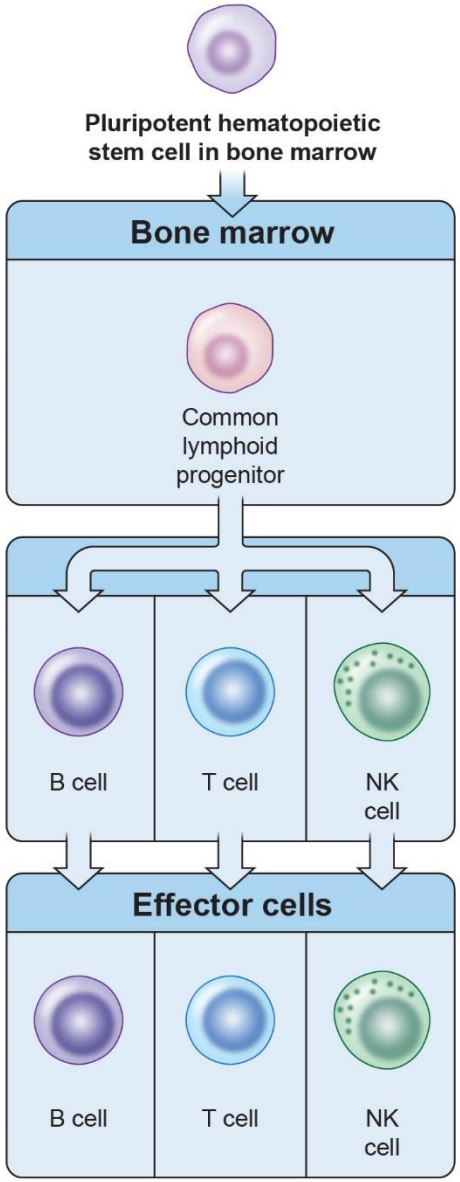
Lymphocytes



B cells
- Produce antibodies that redirect innate immunity

T cells
- Produce cytokines that regulate immunity
- Kill tumor and virus infected cells

Adaptive
(recognize very specific antigens)

Natural Killer (NK) cells
- Kill tumor and virus-infected cells
- Kill antibody-coated cells
- Play dominant role in mediating ADCC in vivo

Innate
(recognize general features)

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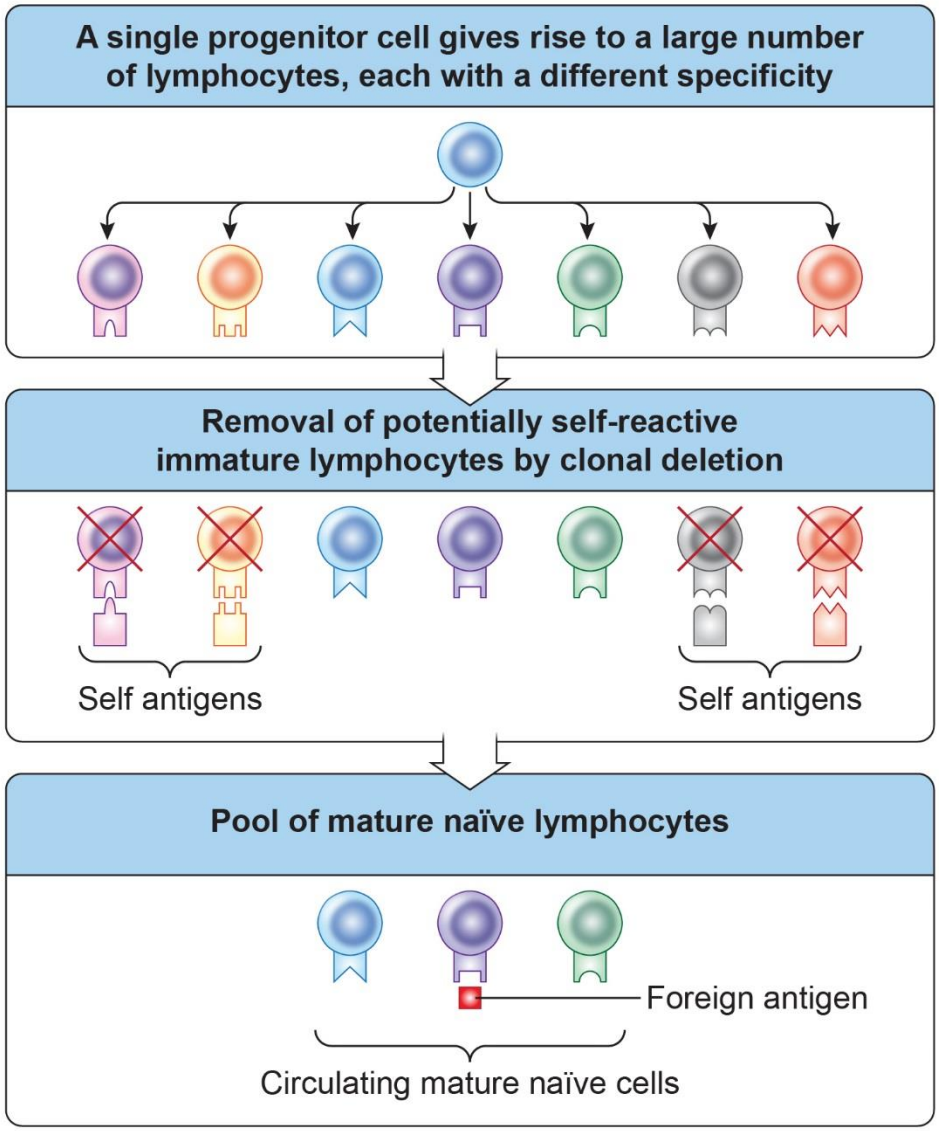
Generating lymphocytes that each have a unique specificity



Generation of vast pool of cells

- Immature cells (non-functional)

Elimination of cells that can recognize self Ags

- One barrier to inducing responses against tumor cells

Mechanism of central tolerance

- Circulating mature naïve cells

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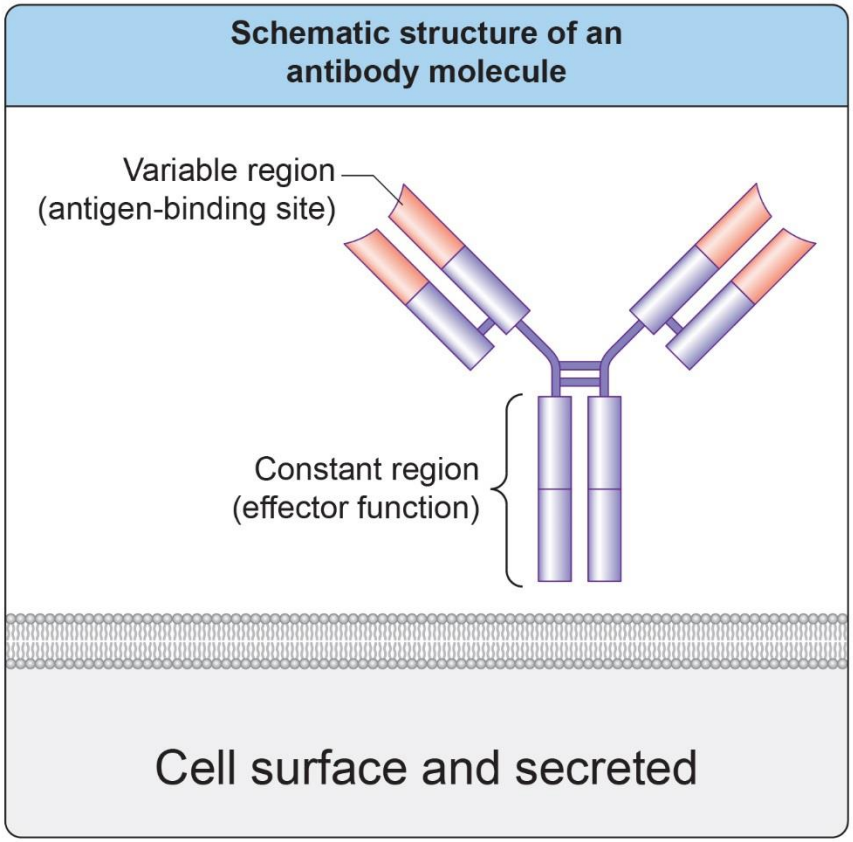
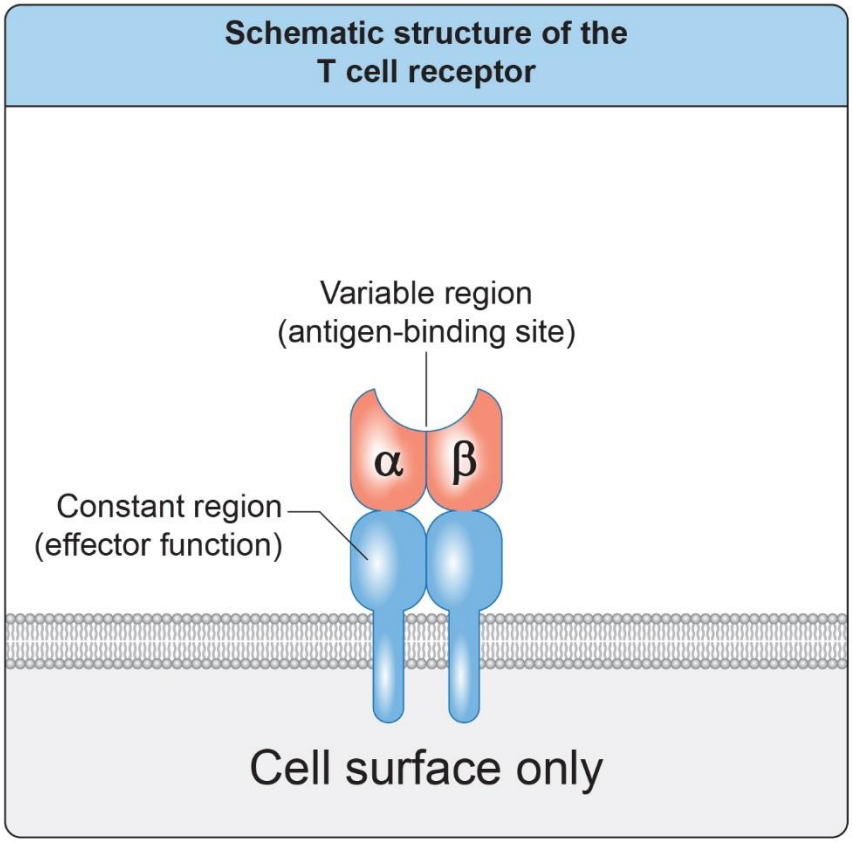
Antigen receptors

Antibody (Ab)

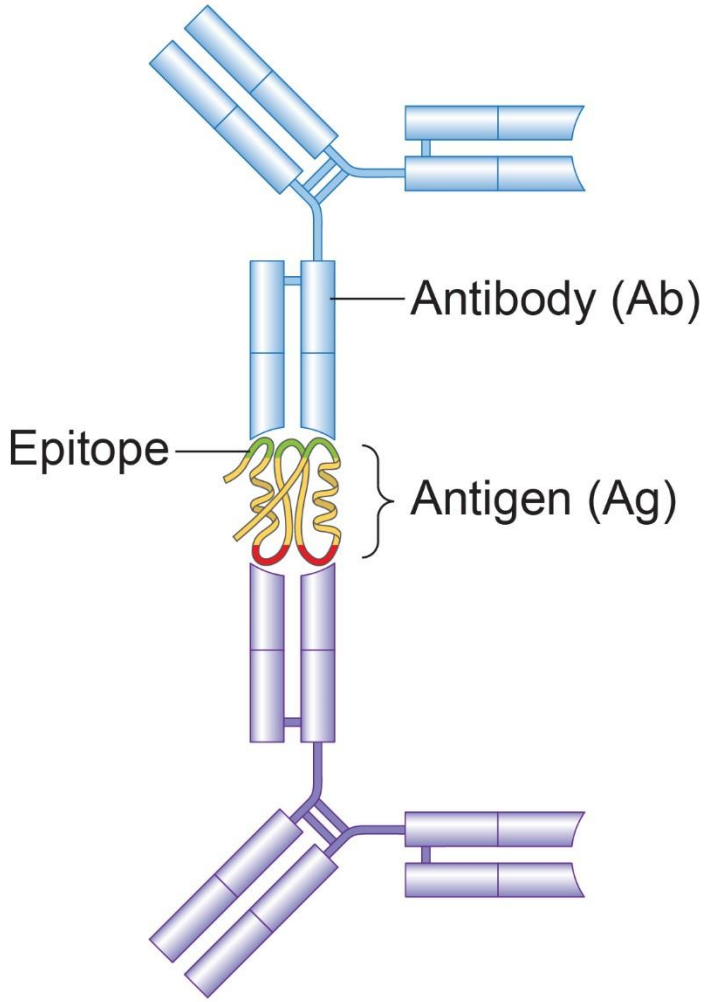


T cell receptor (TCR)

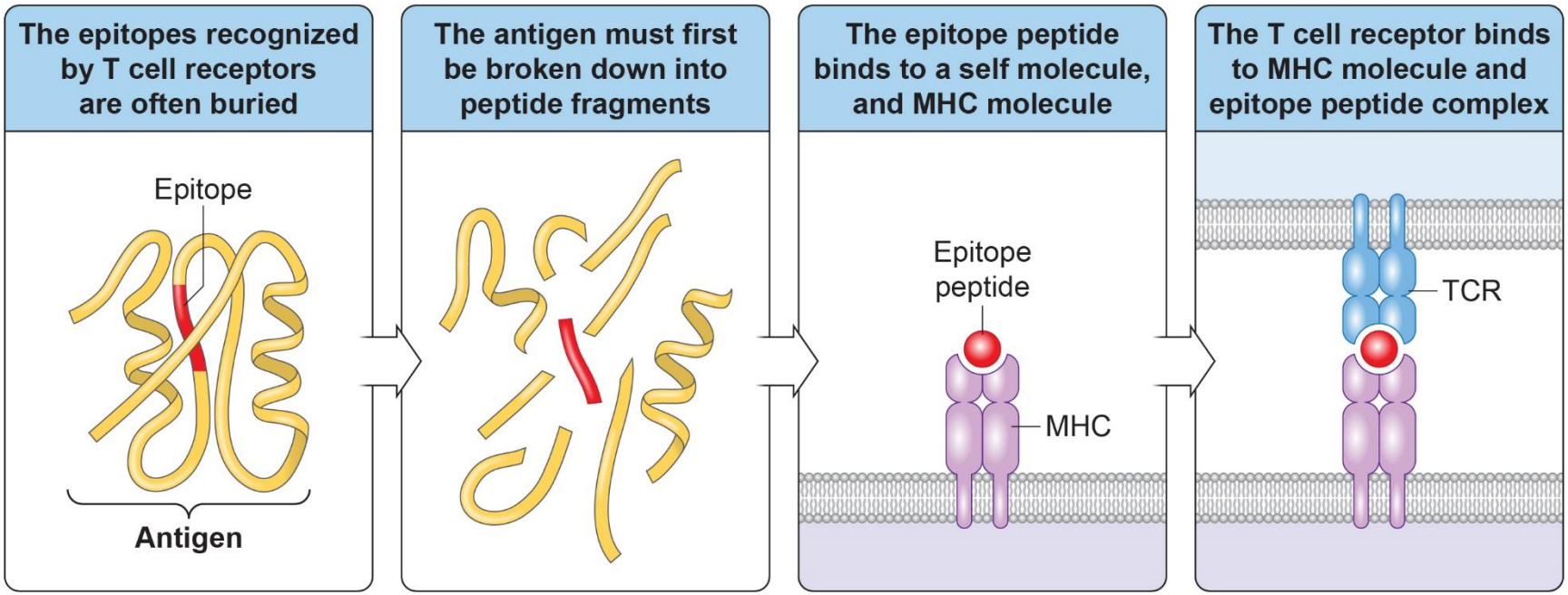


Antigen recognition by antibodies

Ab recognizes portions of proteins in native structures, not processed proteins (may not be continuous portion of protein)



T cell receptors (TCRs) recognize processed proteins presented by MHC



MHC = Major Histocompatibility Complex

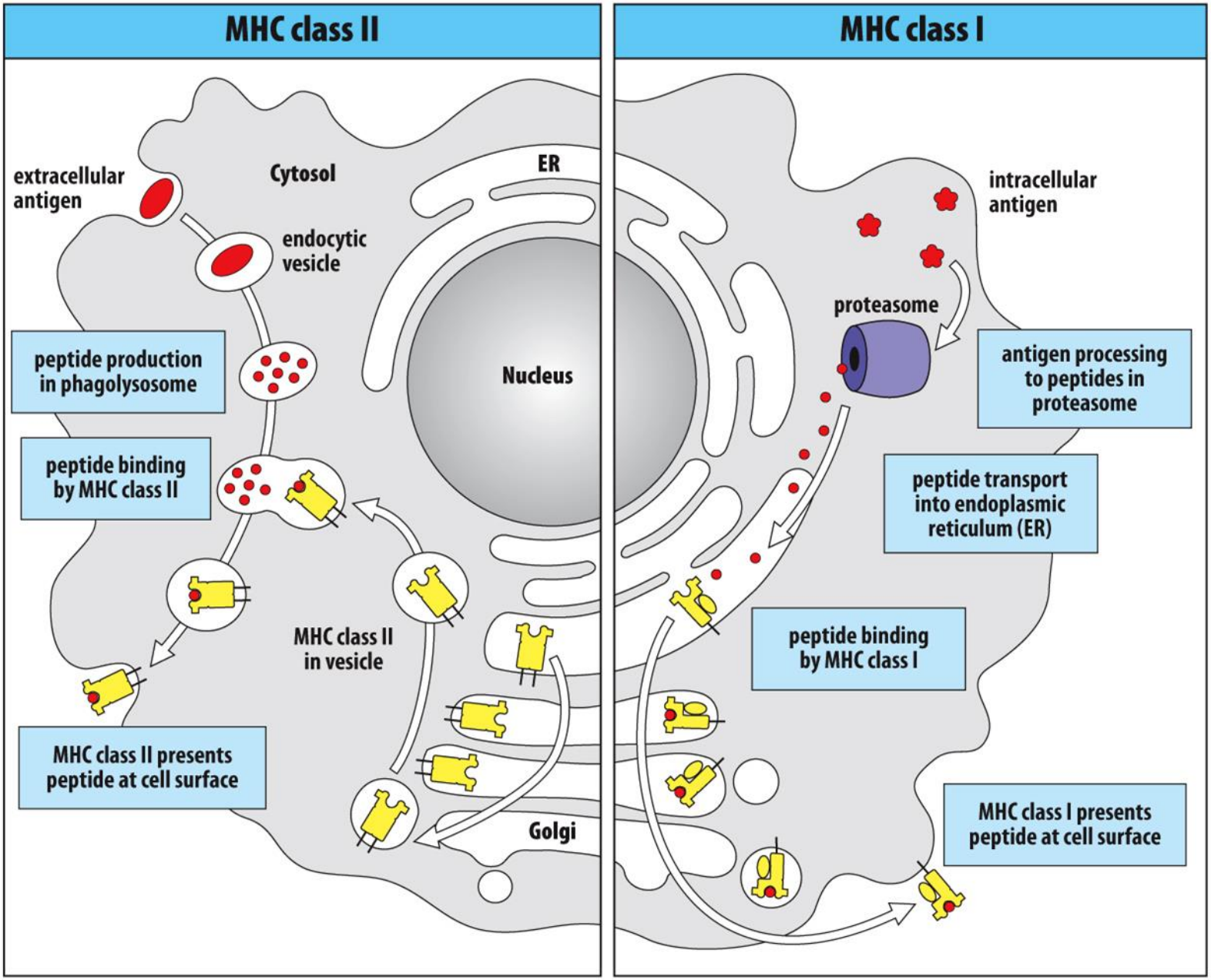


Figure 5.27 The Immune System, 4th ed. (© Garland Science 2015)

Why is T cell recognition of antigen so complicated?

Presentation of peptides by MHC molecules enables T cells to know what's going on inside the cell….

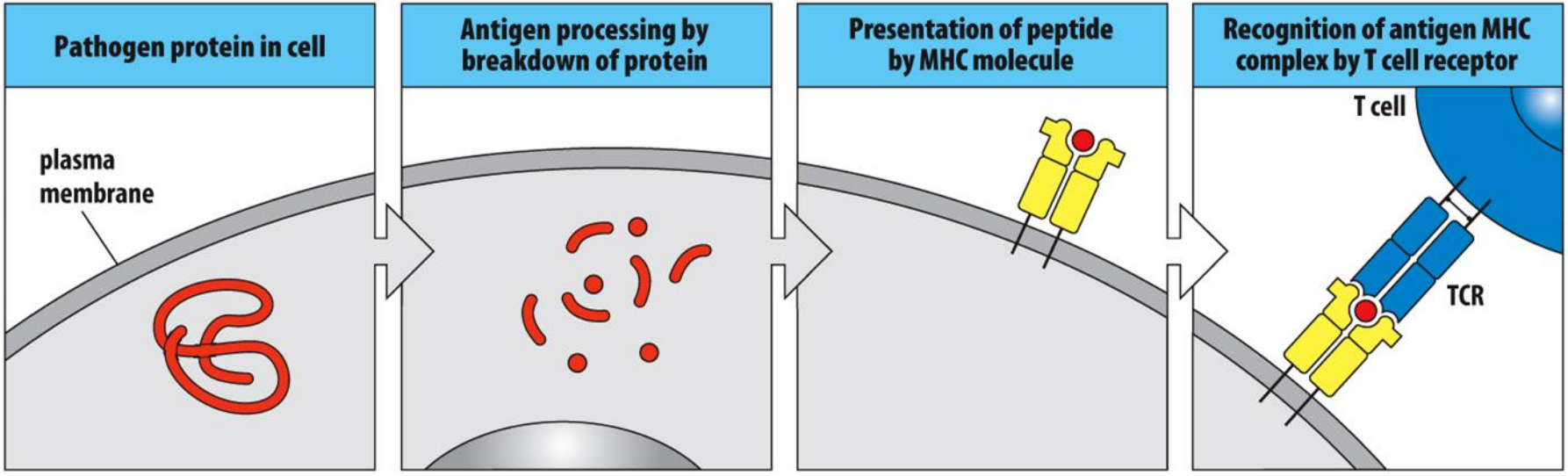
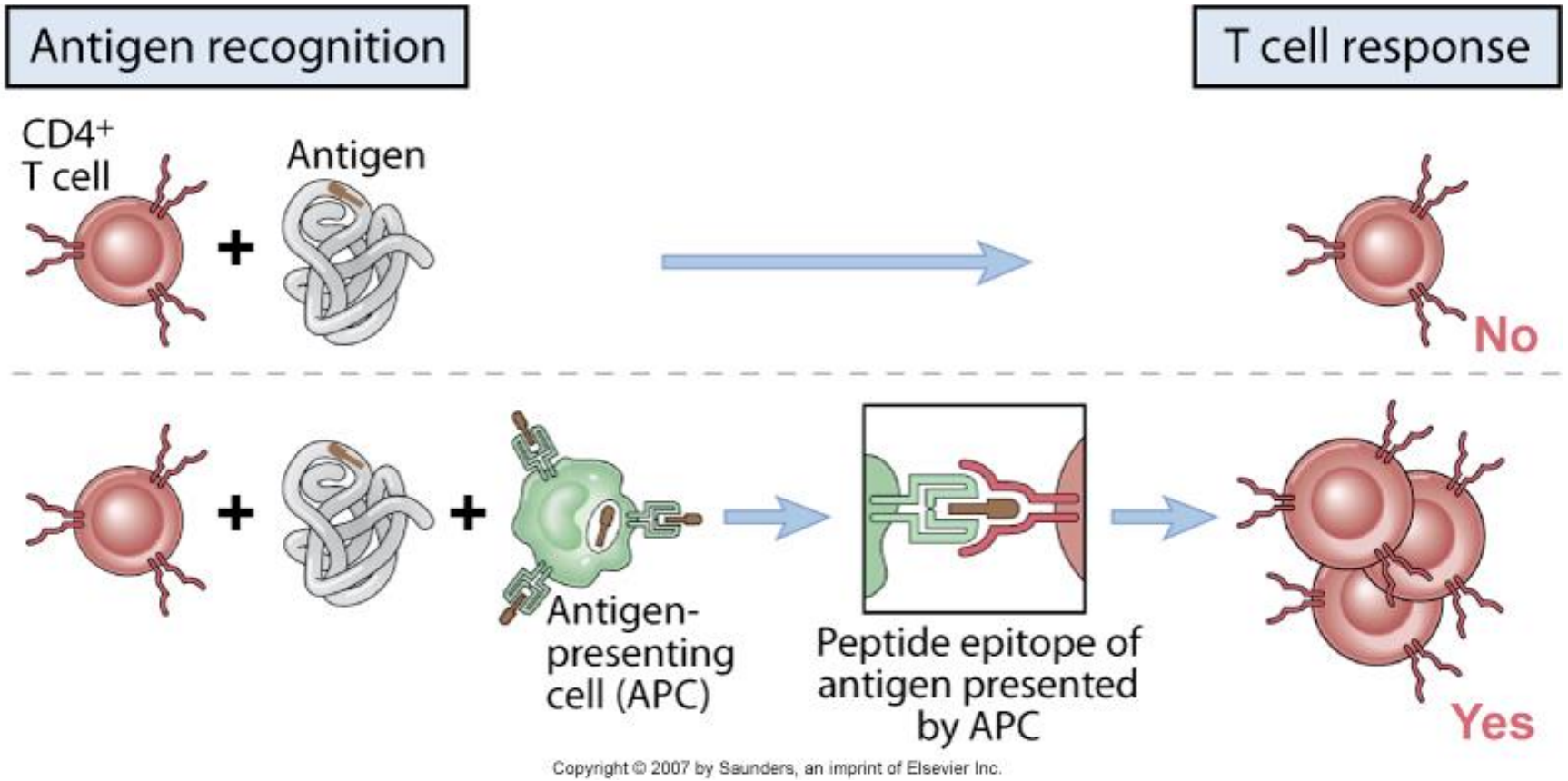


Figure 5.10 The Immune System, 4th ed. (© Garland Science 2015)

…and T cells by necessity have to interact with other cells to be activated, or carry out their function

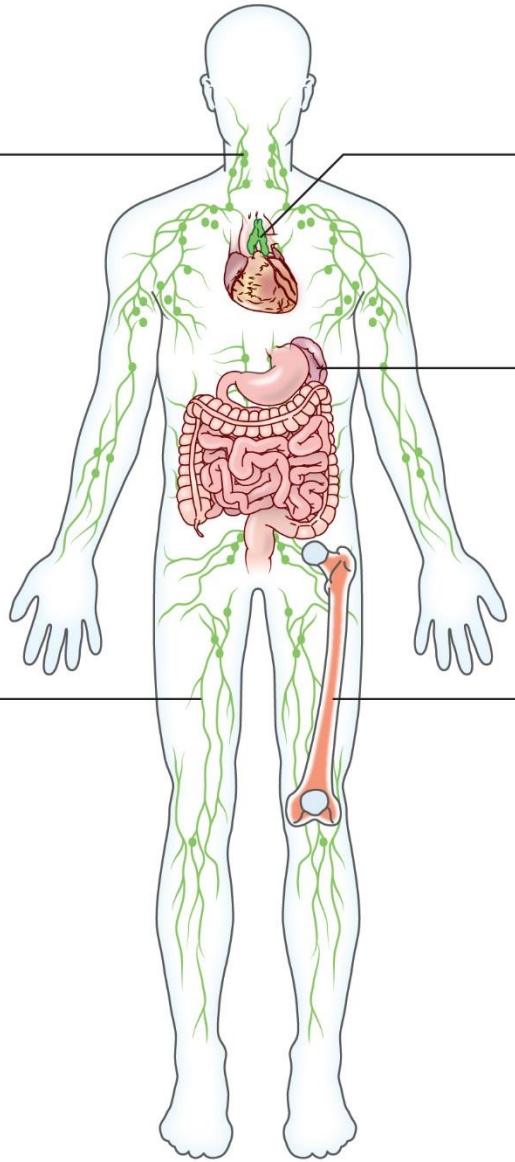


Lymphoid organs

Lymph nodes

Collect lymph and antigen from peripheral sites through lymphatic vessels

Lymphatic vessels



Thymus

Site of T cell development

Spleen

Collects antigens from circulating blood

Bone marrow

Site of myeloid cell and B cell development

Note: Immmune cells and lymphoid aggregates are also found througout the body

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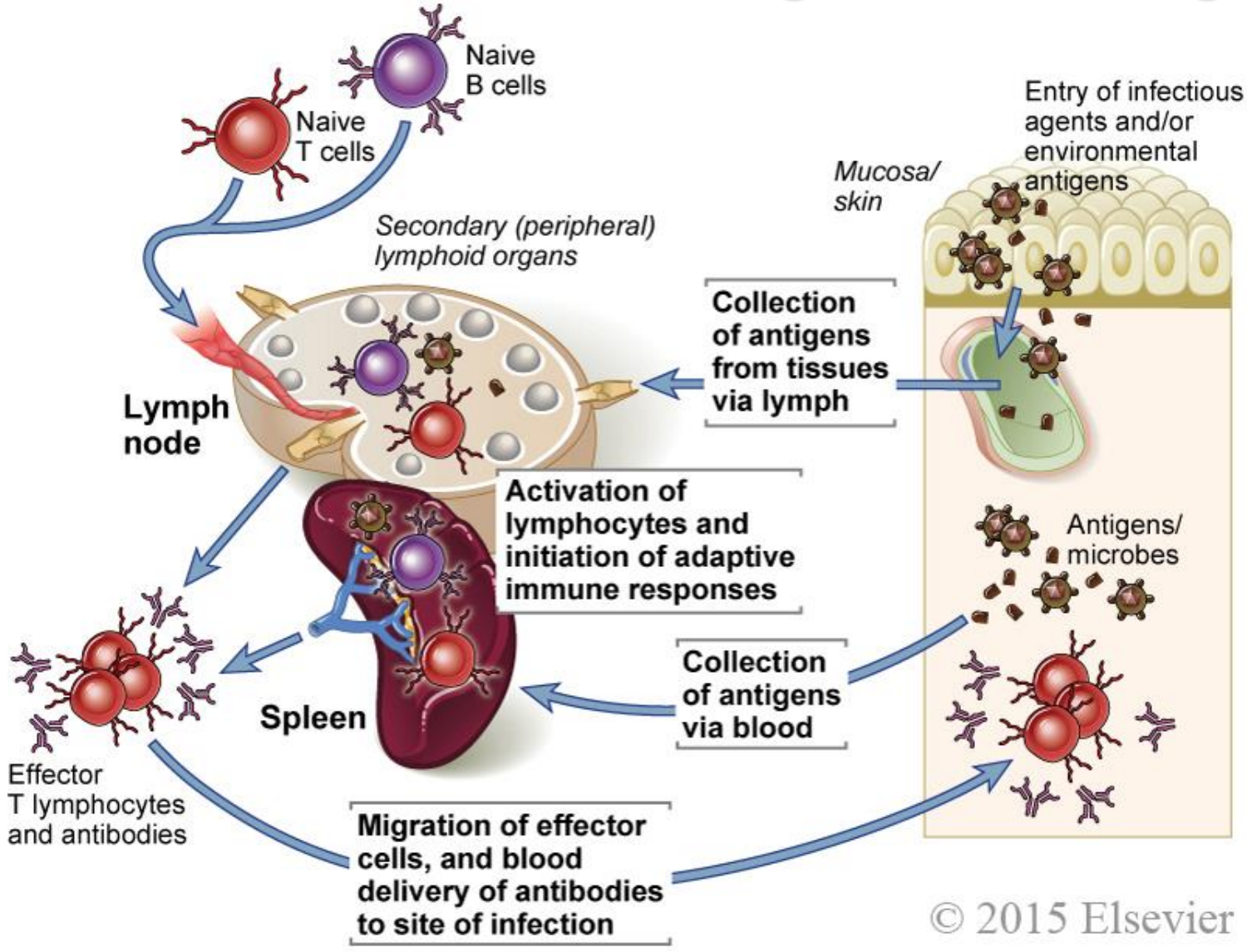
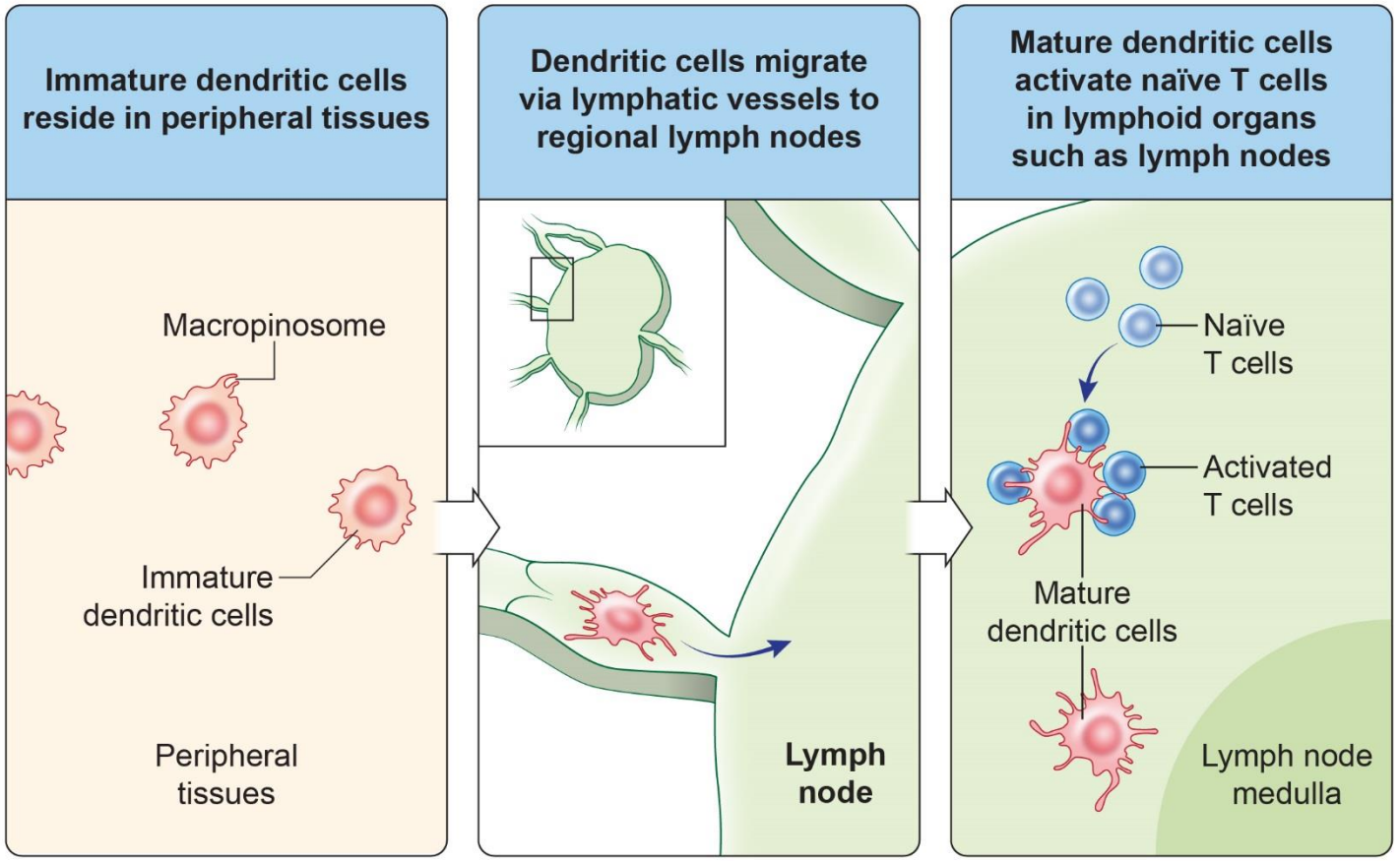
Adaptive immune responses require coordinated localization of T cells and Antigen Presenting Cells

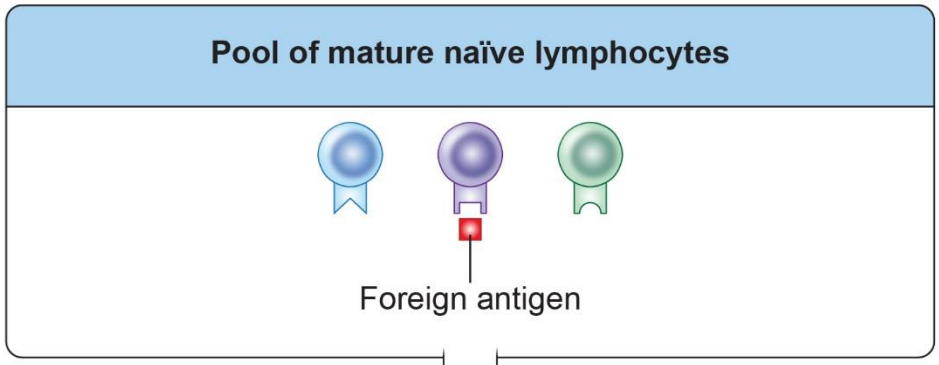


DCs are important for initiating adaptive immune responses



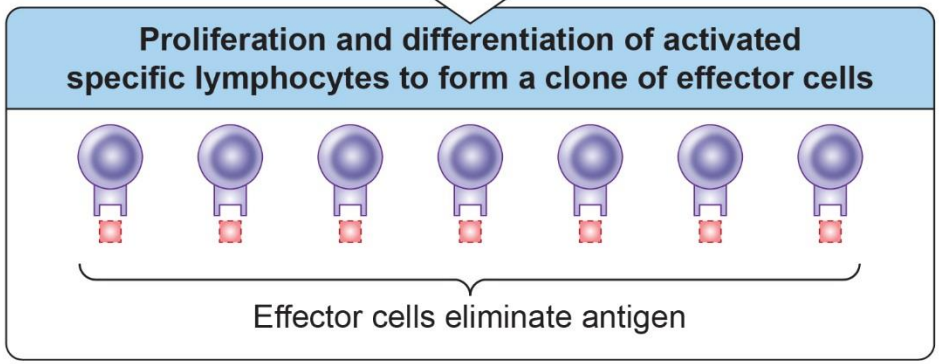
Lymphocyte activation

Naïve



Cells that recognize specific Ag are very rare

Activated or effectors



Results in:
- Expansion
- Acquisition of effector functions

What happens to T cells and B cells after immune response?

Differentiate into long-lived memory lymphocytes

Three signals are necessary for naïve T cells to differentiate into effector (or memory) cells

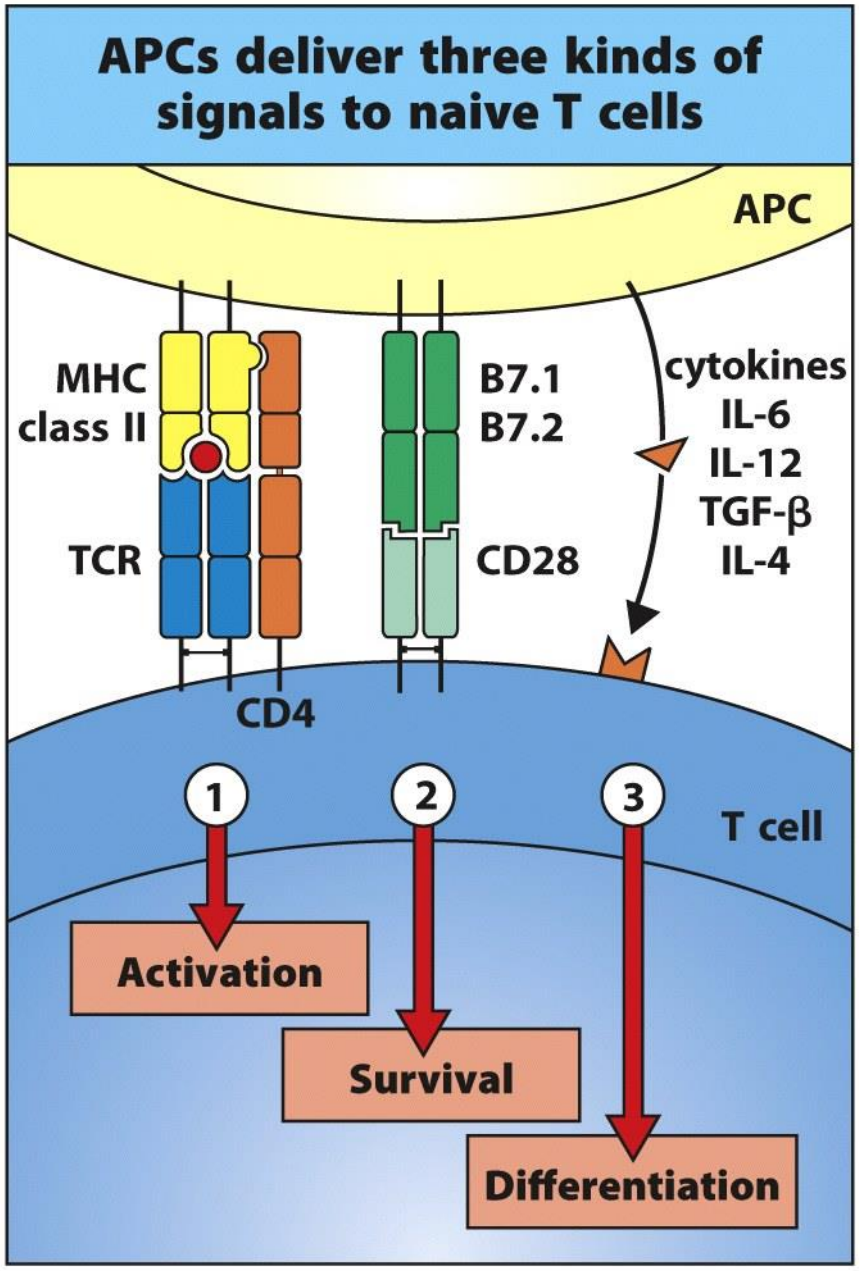
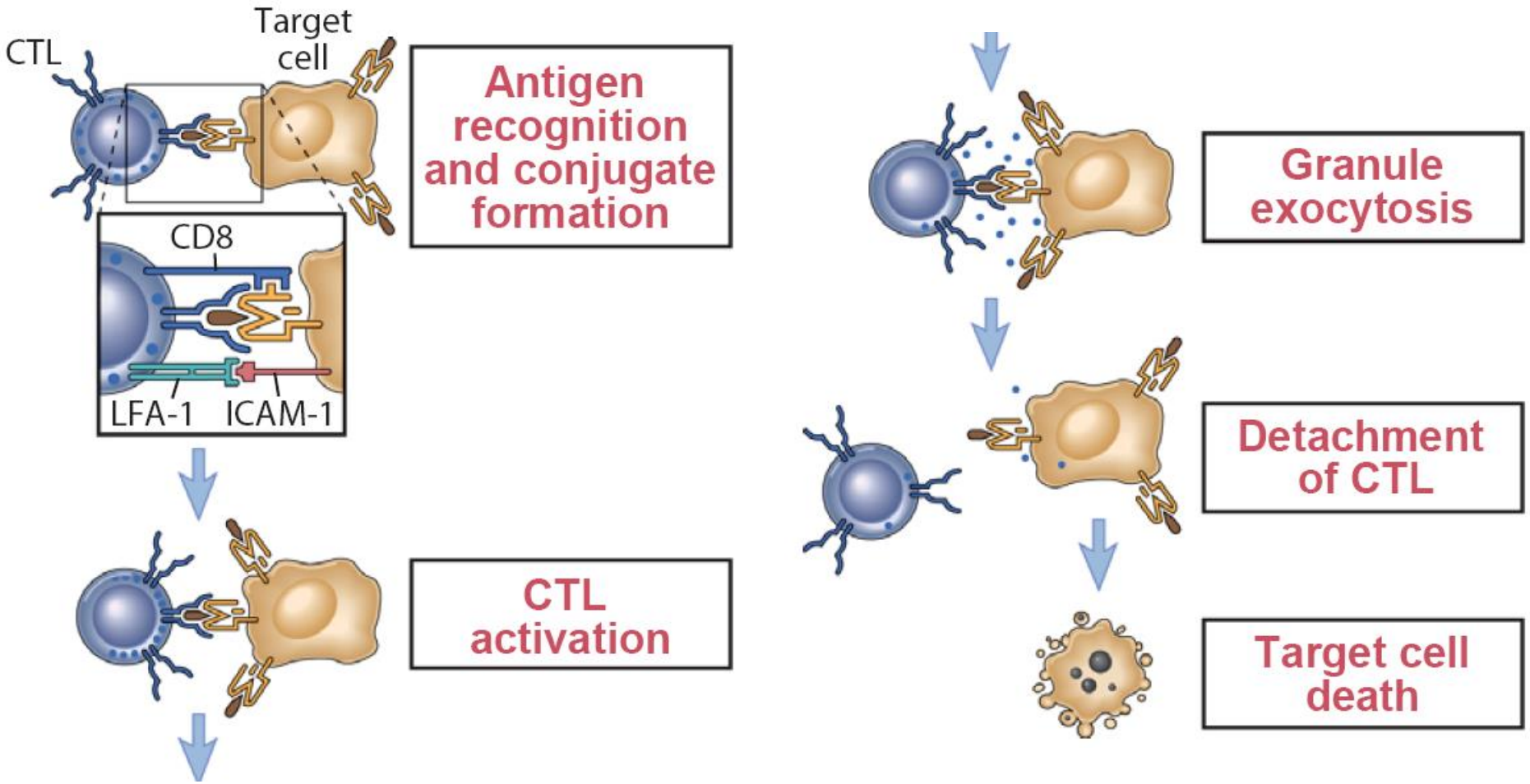


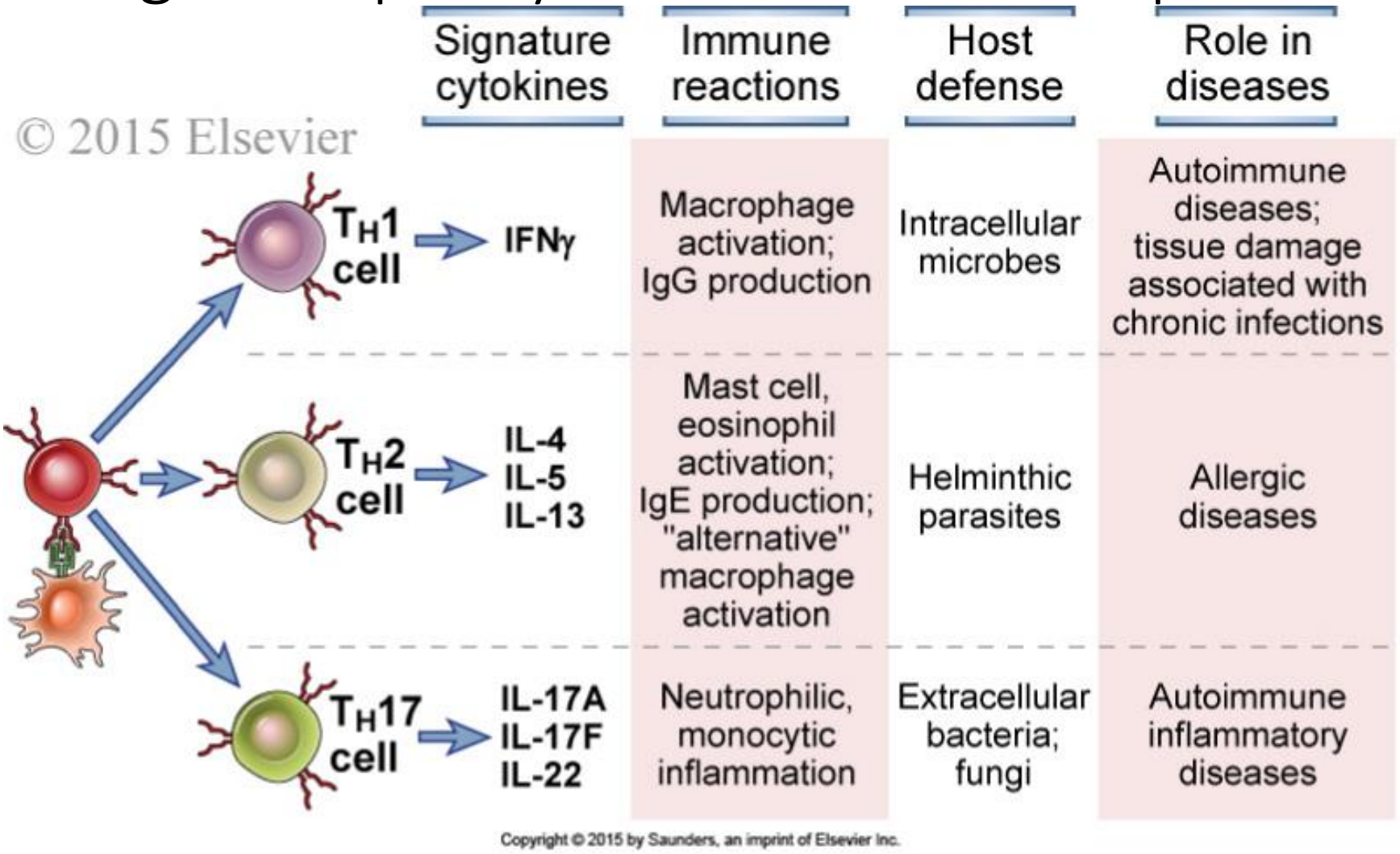
Figure 9.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Effector CD8 T cells kill other cells (and also release proinflammatory cytokines)



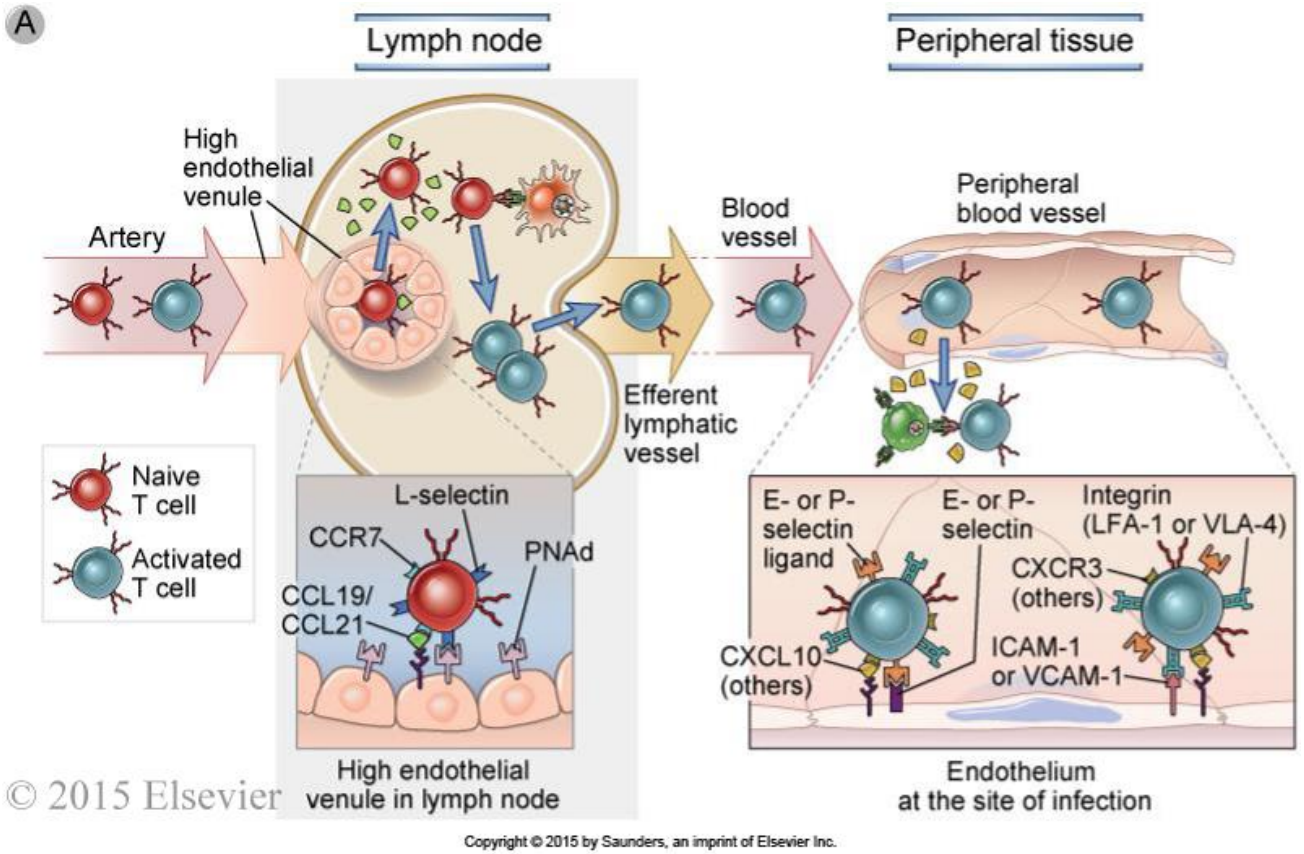
Activated CD8 T cells do not require costimulation for killing
They are “serial killers” - move on to the next target

Effector CD4 T cells come in many flavors that regulate quality of the immune response



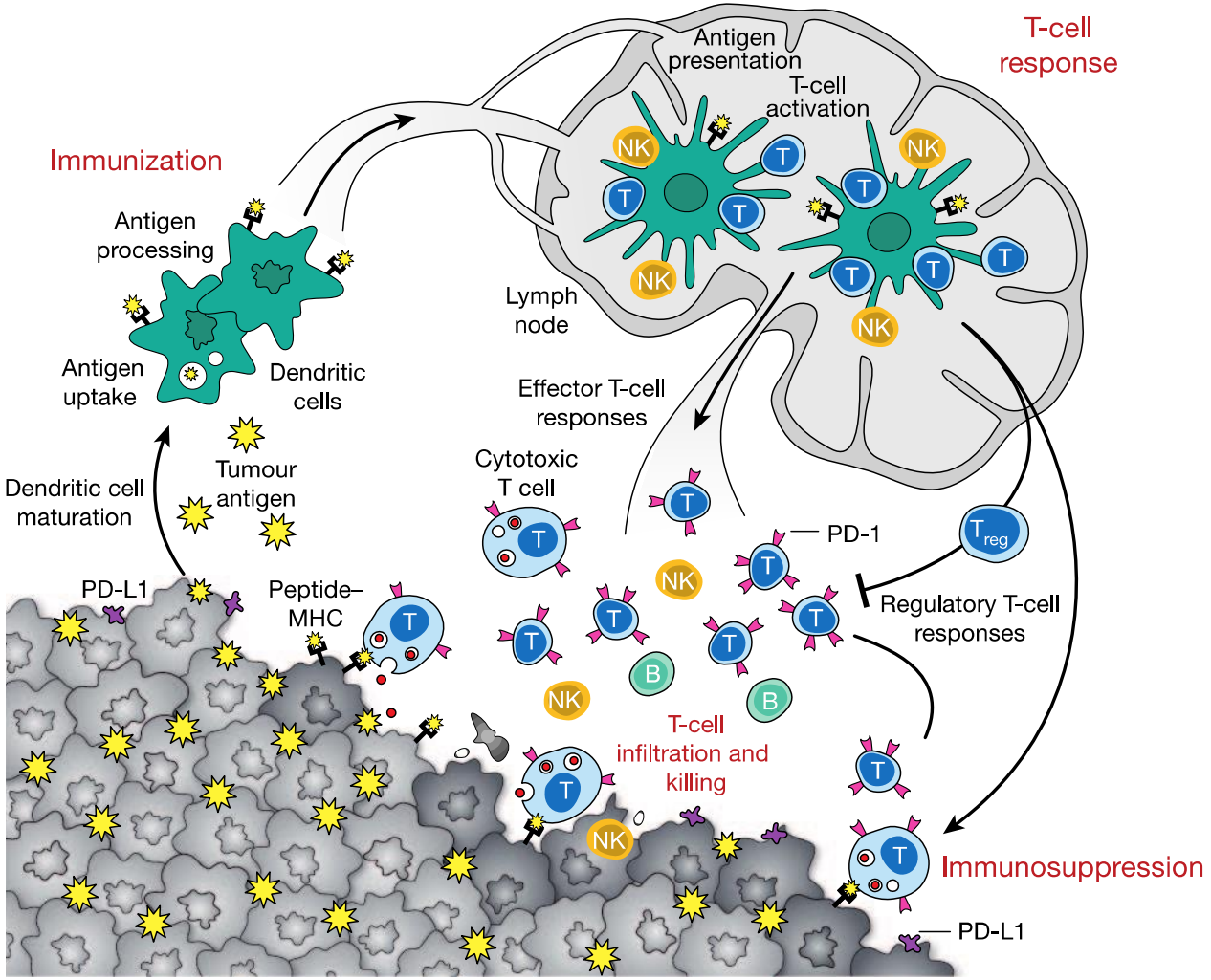
Differentiation along these pathways is controlled by cytokines released by APC or other innate cells

Changes in lymphocyte homing receptor expression and trafficking accompany activation



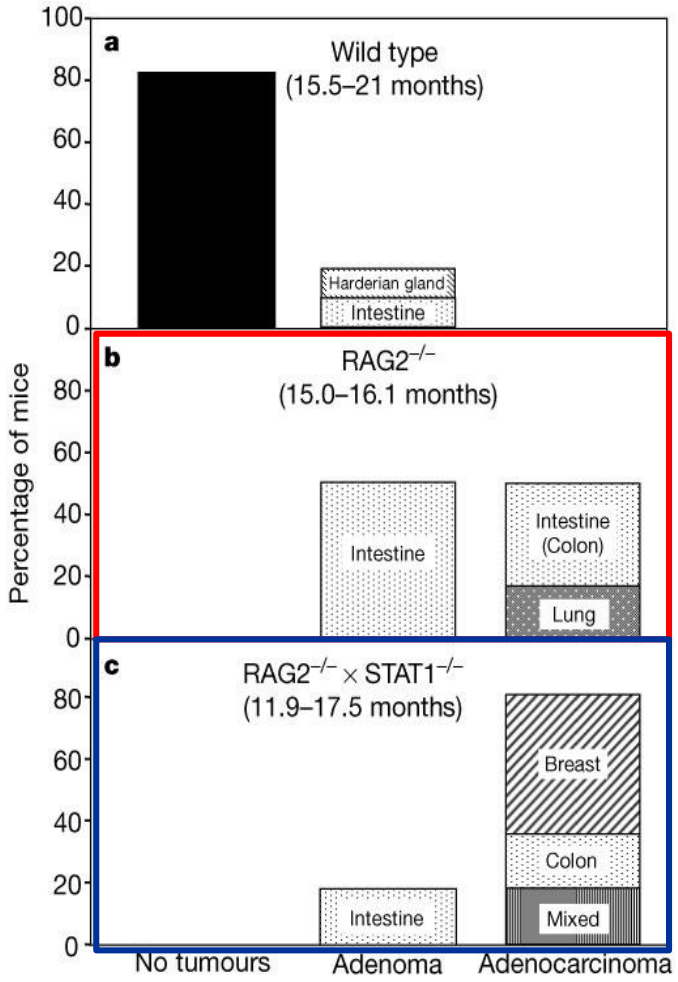
- Homing receptors on T cells and ligands on the vasculature regulate the entry of naïve T cells into lymph nodes
- Activation changes the pattern of homing receptor expression to enable effector T cells to enter inflamed peripheral tissue

Elements of the immune system involved in the immune response to cancer



Mellman et al. (2011) Nature. 480: 480-489

Immunosurveillance: The immune response controls the outgrowth of spontaneous colorectal tumors



Normal Immune System:
80% of mice are disease-free
none have cancer

Elimination of adaptive immunity:
0% of mice are disease-free
50% have cancer

Elimination of innate and adaptive immunity: 0% of mice are disease-free
80% have cancer

Shankaran *et al*., Nature 410. 2001.

Risk of infection-related malignancies is increased significantly in US transplant recipients

Viruses: Epstein-Barr, Human papilloma, hepatitis B and C, Herpes simplex B

Cancer Site	No. of Cases		SIR (95% CI)	*P* Value	Incidence/100 000 Person-Years[a]		EAR/100 000 Person-Years (95% CI)
	Observed	Expected			Observed	Expected	
Non-Hodgkin lymphoma	1504	199.4	7.54 (7.17 to 7.93)	<.001	194.0	25.7	168.3 (158.6 to 178.4)
Nodal	831	136.6	6.08 (5.68 to 6.51)	<.001	107.2	17.6	89.6 (82.4 to 97.1)
Extranodal	673	62.8	10.72 (9.93 to 11.56)	<.001	86.8	8.1	78.7 (72.3 to 85.5)
Liver	930	80.5	11.56 (10.83 to 12.33)	<.001	120.0	10.4	109.6 (102.0 to 117.6)
Stomach	152	90.9	1.67 (1.42 to 1.96)	<.001	19.6	11.7	7.9 (4.9 to 11.3)
Kaposi sarcoma	120	2.0	61.46 (50.95 to 73.49)	<.001	15.5	0.3	15.2 (12.6 to 18.3)
Oropharynx including tonsil	106	52.8	2.01 (1.64 to 2.43)	<.001	13.7	6.8	6.9 (4.4 to 9.7)
Anus	90	15.4	5.84 (4.70 to 7.18)	<.001	11.6	2.0	9.6 (7.3 to 12.3)
Hodgkin lymphoma	85	23.7	3.58 (2.86 to 4.43)	<.001	11.0	3.1	7.9 (5.7 to 10.5)
Vulva	58	7.6	7.60 (5.77 to 9.83)	<.001	7.5	1.0	6.5 (4.7 to 8.7)
Cervix	45	43.6	1.03 (0.75 to 1.38)	.88	5.8	5.6	0.2 (–1.4 to 2.1)
Penis	22	5.3	4.13 (2.59 to 6.26)	<.001	2.8	0.7	2.2 (1.1 to 3.6)
Nasopharynx	8	8.3	0.96 (0.42 to 1.90)	>.99	1.0	1.1	0 (–0.6 to 1.0)
Vagina	7	3.0	2.35 (0.94 to 4.84)	.07	0.9	0.4	0.5 (0 to 1.5)
Total[b]	10 656	5080.6	2.10 (2.06 to 2.14)	<.001	1374.7	655.4	719.3 (693.3 to 745.6)

Abbreviations: EAR, excess absolute risk; SIR, standardized incidence ratio.

[a] Includes invasive cancers arising during 775 147 person-years. Incidence is presented for the entire cohort, but can be calculated separately for males or females for sex-specific malignancies based on follow-up of 465 521 person-years in males and 309 626 person-years in females. Cancer types are listed in order of decreasing frequency.

[b] Includes non–infection-related malignancies presented in Table 3.

From: **Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients**
JAMA. 2011;306(17):1891-1901. doi:10.1001/jama.2011.1592

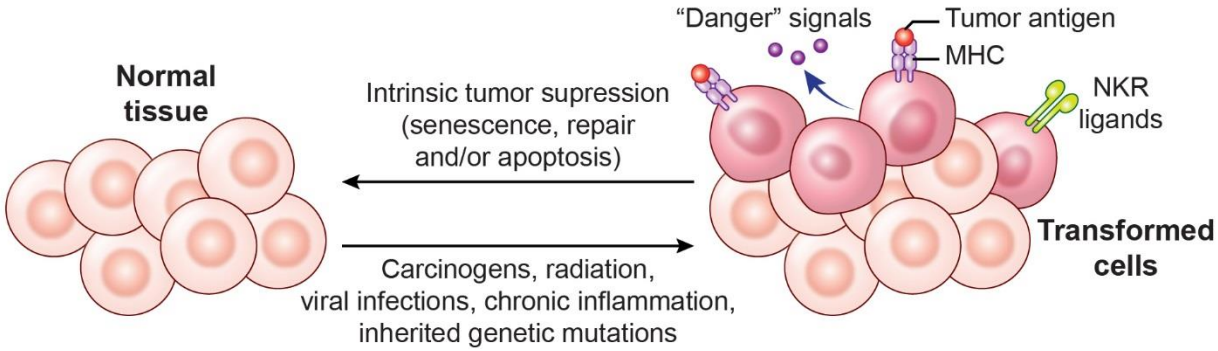
Risk of *non*-infection-related malignancies is increased significantly in US transplant recipients

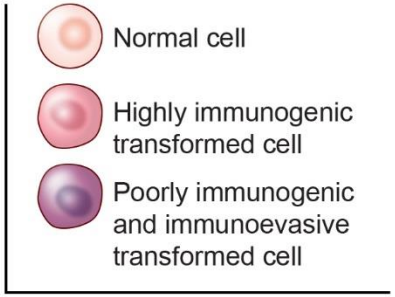
Cancer Site	No. of Cases		SIR (95% CI)	*P* Value	Incidence/100 000 Person-Years[a]		EAR/100 000 Person-Years (95% CI)
	Observed	Expected			Observed	Expected	
Lung	1344	682.8	1.97 (1.86 to 2.08)	<.001	173.4	88.1	85.3 (76.2 to 94.8)
Prostate	1039	1126.9	0.92 (0.87 to 0.98)	.009	134.0	145.4	−11.3 (−19.4 to −2.9)
Kidney	752	161.8	4.65 (4.32 to 4.99)	<.001	97.0	20.9	76.1 (69.3 to 83.3)
Colorectum	627	504.9	1.24 (1.15 to 1.34)	<.001	80.9	65.1	15.8 (9.5 to 22.3)
Breast	481	567.9	0.85 (0.77 to 0.93)	<.001	62.1	73.3	−11.2 (−16.6 to −5.4)
Melanoma	381	160.3	2.38 (2.14 to 2.63)	<.001	49.2	20.7	28.5 (23.7 to 33.7)
Thyroid	238	80.8	2.95 (2.58 to 3.34)	<.001	30.7	10.4	20.3 (16.5 to 24.4)
Urinary bladder	225	148.1	1.52 (1.33 to 1.73)	<.001	29.0	19.1	9.9 (6.2 to 14.0)
Skin (nonmelanoma, nonepithelial)	184	13.3	13.85 (11.92 to 16.00)	<.001	23.7	1.7	22.0 (18.7 to 25.7)
Pancreas	157	107.3	1.46 (1.24 to 1.71)	<.001	20.3	13.8	6.4 (3.4 to 9.8)
Other oral cavity and pharynx	149	58.2	2.56 (2.17 to 3.01)	<.001	19.2	7.5	11.7 (8.8 to 15.1)
Lip	130	7.7	16.78 (14.02 to 19.92)	<.001	16.8	1.0	15.8 (13.0 to 18.9)
Plasma cell neoplasms	118	64.3	1.84 (1.52 to 2.20)	<.001	15.2	8.3	6.9 (4.3 to 9.9)
Acute myeloid leukemia	102	33.9	3.01 (2.45 to 3.65)	<.001	13.2	4.4	8.8 (6.4 to 11.6)
Larynx	97	60.8	1.59 (1.29 to 1.95)	<.001	12.5	7.8	4.7 (2.3 to 7.4)
Esophagus	96	61.5	1.56 (1.26 to 1.91)	<.001	12.4	7.9	4.4 (2.1 to 7.2)
Uterine corpus	94	109.3	0.86 (0.70 to 1.05)	.15	12.1	14.1	−2.0 (−4.3 to 0.7)
Soft tissue including heart	65	28.8	2.25 (1.74 to 2.87)	<.001	8.4	3.7	4.7 (2.8 to 7.0)
Salivary gland	56	12.3	4.55 (3.44 to 5.91)	<.001	7.2	1.6	5.6 (3.9 to 7.8)
Ovary	54	56.7	0.95 (0.72 to 1.24)	.79	7.0	7.3	−0.3 (−2.1 to 1.8)
Small intestine	50	20.6	2.43 (1.80 to 3.20)	<.001	6.5	2.7	3.8 (2.1 to 5.8)
Brain	45	59.6	0.76 (0.55 to 1.01)	.06	5.8	7.7	−1.9 (−3.5 to 0.1)
Testis	40	20.4	1.96 (1.40 to 2.67)	<.001	5.2	2.6	2.5 (1.1 to 4.4)
Other biliary	39	15.9	2.45 (1.74 to 3.35)	<.001	5.0	2.1	3.0 (1.5 to 4.8)
Intrahepatic bile duct	38	6.6	5.76 (4.08 to 7.91)	<.001	4.9	0.9	4.1 (2.6 to 5.9)
Chronic myeloid leukemia	38	10.9	3.47 (2.46 to 4.77)	<.001	4.9	1.4	3.5 (2.1 to 5.3)
Chronic lymphocytic leukemia	23	38.9	0.59 (0.38 to 0.89)	.008	3.0	5.0	−2.0 (−3.1 to −0.6)
Gallbladder	22	11.0	2.00 (1.25 to 3.02)	.005	2.8	1.4	1.4 (0.4 to 2.9)
Eye and orbit	21	7.6	2.78 (1.72 to 4.24)	<.001	2.7	1.0	1.7 (0.7 to 3.2)
Renal pelvis	17	8.3	2.05 (1.20 to 3.29)	.01	2.2	1.1	1.1 (0.2 to 2.4)
Acute lymphocytic leukemia	17	8.2	2.06 (1.20 to 3.30)	.01	2.2	1.1	1.1 (0.2 to 2.4)
Mesothelioma	15	11.5	1.30 (0.73 to 2.15)	.37	1.9	1.5	0.4 (−0.4 to 1.7)
Bones and joints	14	7.1	1.98 (1.09 to 3.33)	.03	1.8	0.9	0.9 (0.1 to 2.1)
Other acute leukemia	5	2.3	2.20 (0.71 to 5.13)	.16	0.6	0.3	0.4 (−0.1 to 1.2)
Acute monocytic leukemia	4	1.7	2.35 (0.64 to 6.01)	.19	0.5	0.2	0.3 (−0.1 to 1.1)
Miscellaneous specified malignancies	546	172.1	3.17 (2.91 to 3.45)	<.001	70.4	22.2	48.2 (42.4 to 54.4)
Tumors with poorly specified histology	206	97.9	2.11 (1.83 to 2.41)	<.001	26.6	12.6	14.0 (10.4 to 17.8)
Total[b]	10 656	5080.6	2.10 (2.06 to 2.14)	<.001	1374.7	655.4	719.3 (693.3 to 745.6)

Abbreviations: EAR, excess absolute risk; SIR, standardized incidence ratio.
[a] Includes invasive cancers arising during 775 147 person-years. Incidence is presented for the entire cohort, but can be calculated separately for males or females for sex-specific malignancies based on follow-up of 465 521 person-years in males and 309 626 person-years in females. Cancer types are listed in order of decreasing frequency.
[b] Includes infection-related malignancies presented in Table 2.

From: **Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients**
JAMA. 2011;306(17):1891-1901. doi:10.1001/jama.2011.1592

The 3 Es of cancer immunoediting





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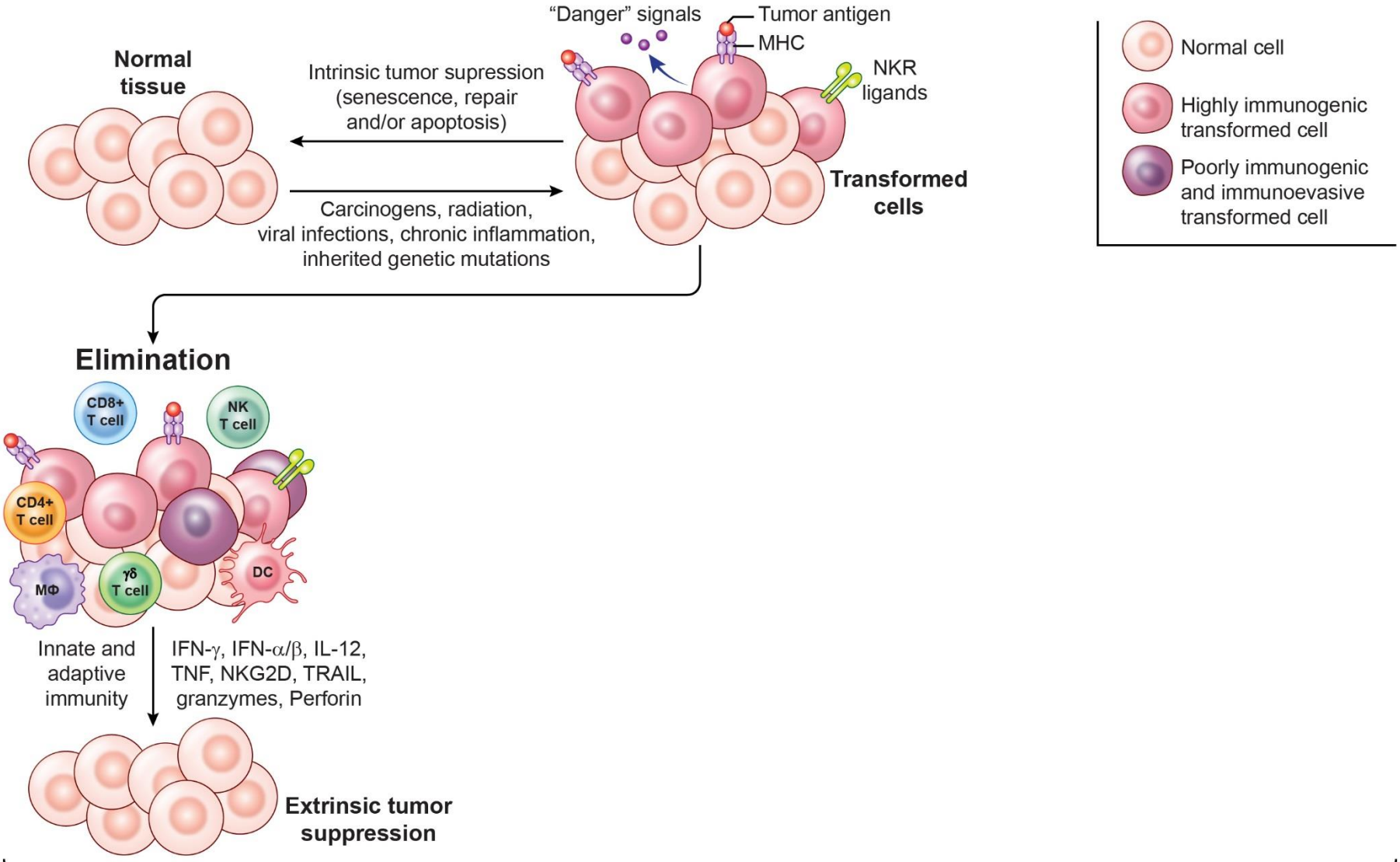
The 3 Es of cancer immunoediting



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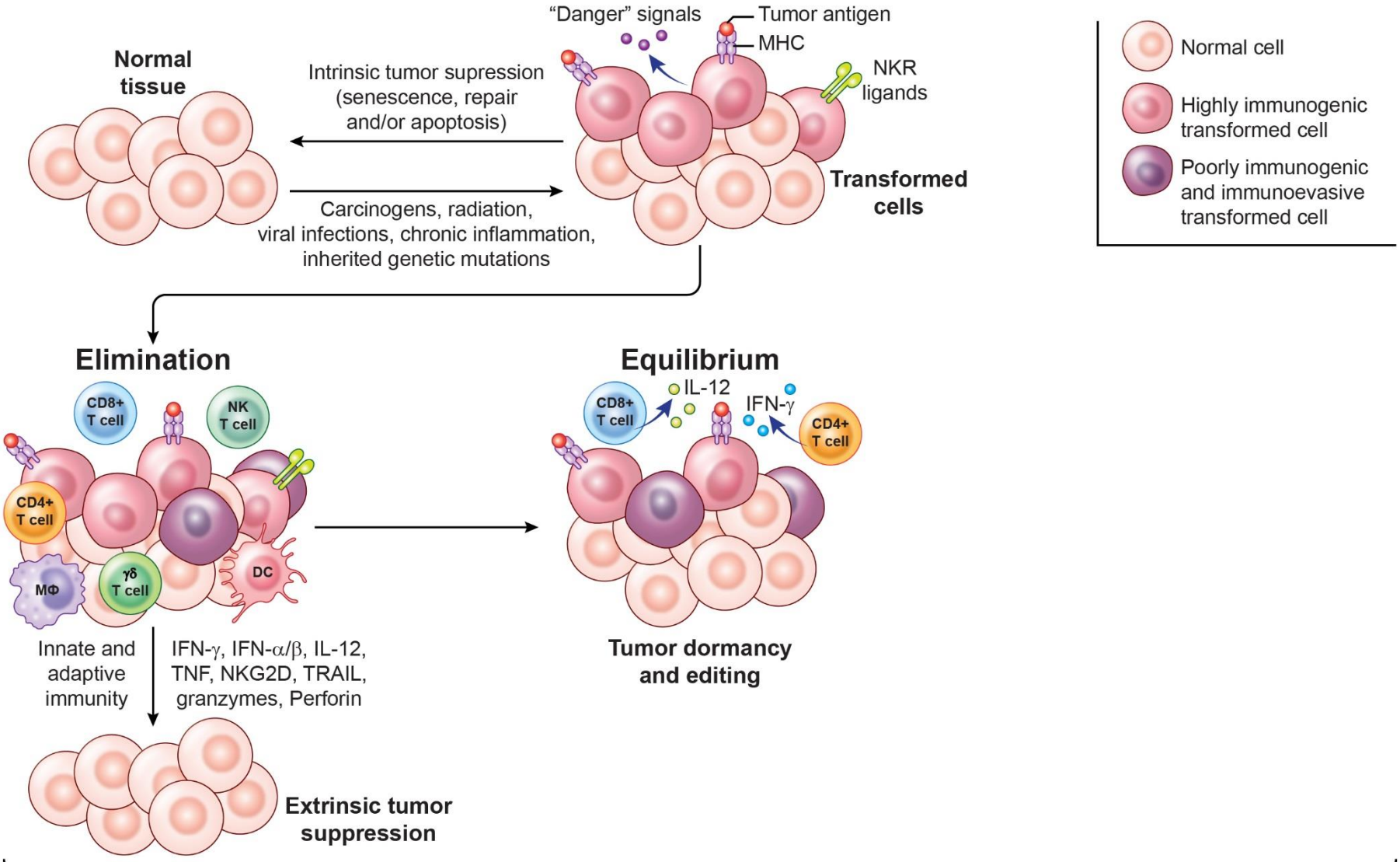
The 3 Es of cancer immunoediting



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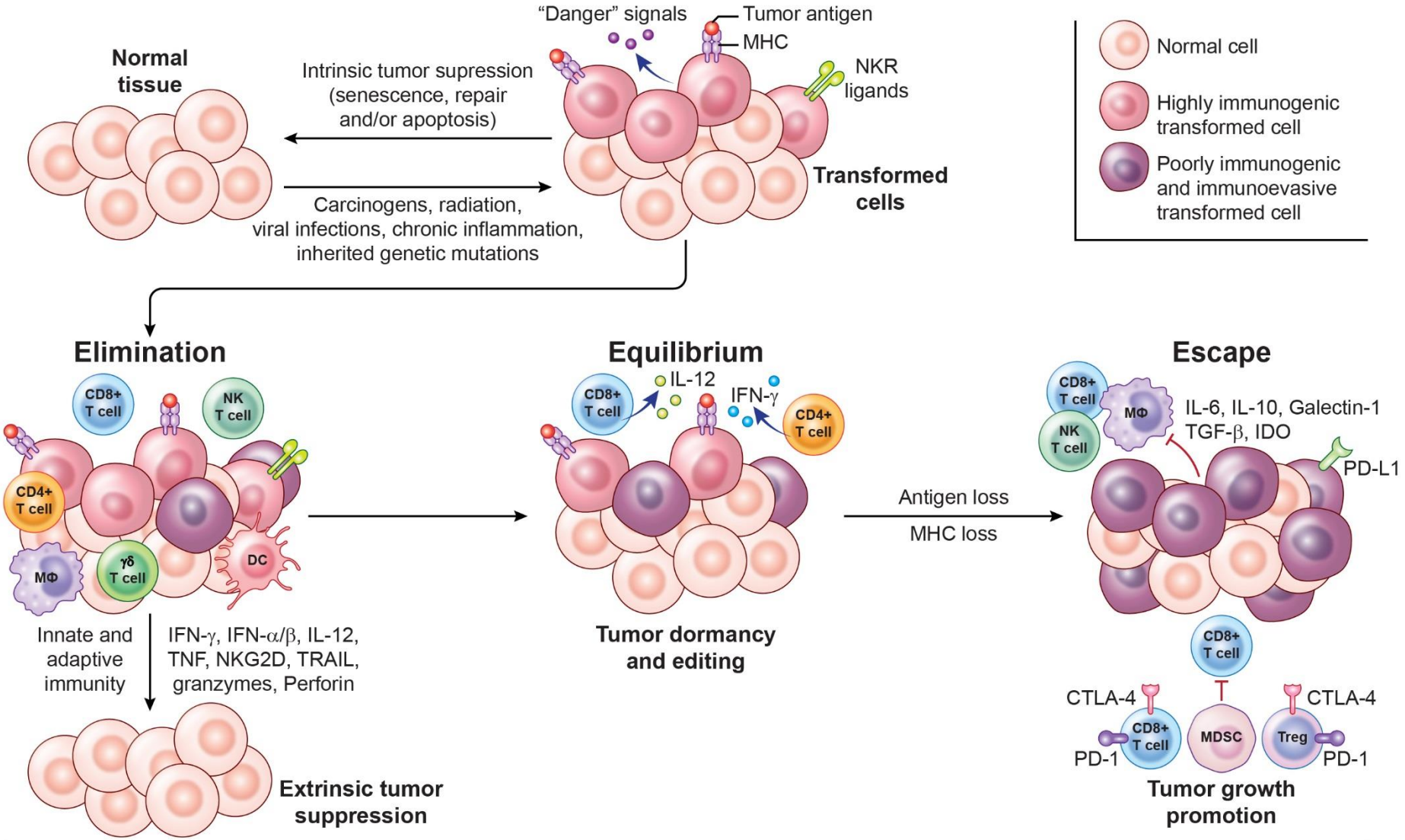

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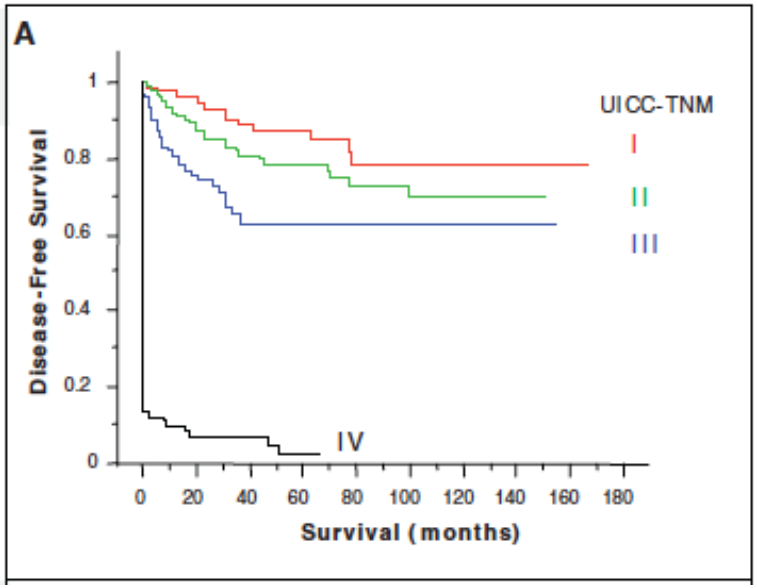
Tumor infiltrating lymphocytes predict survival in colorectal cancer better than Duke's staging

Tumor histopathology

UICC-TNM Staging system

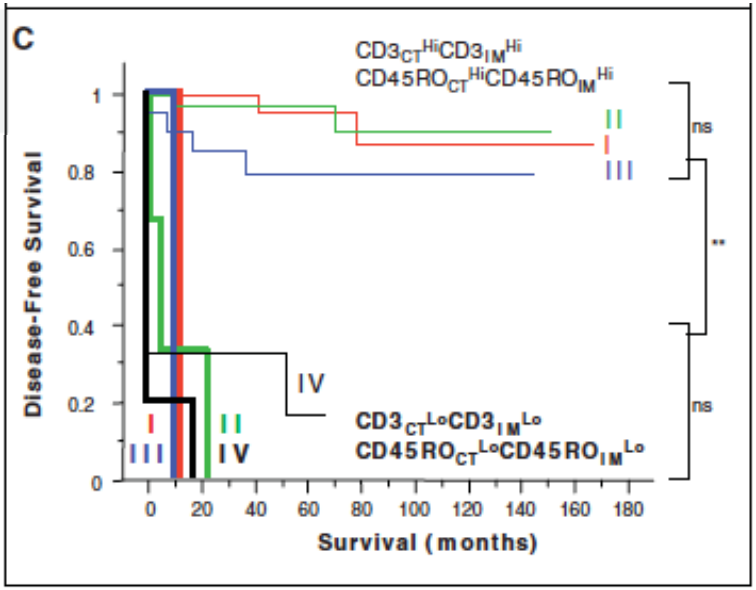


Tumor infiltrating immune cells

$CD3_{CT}CD3_{IM}$ evaluation

plus

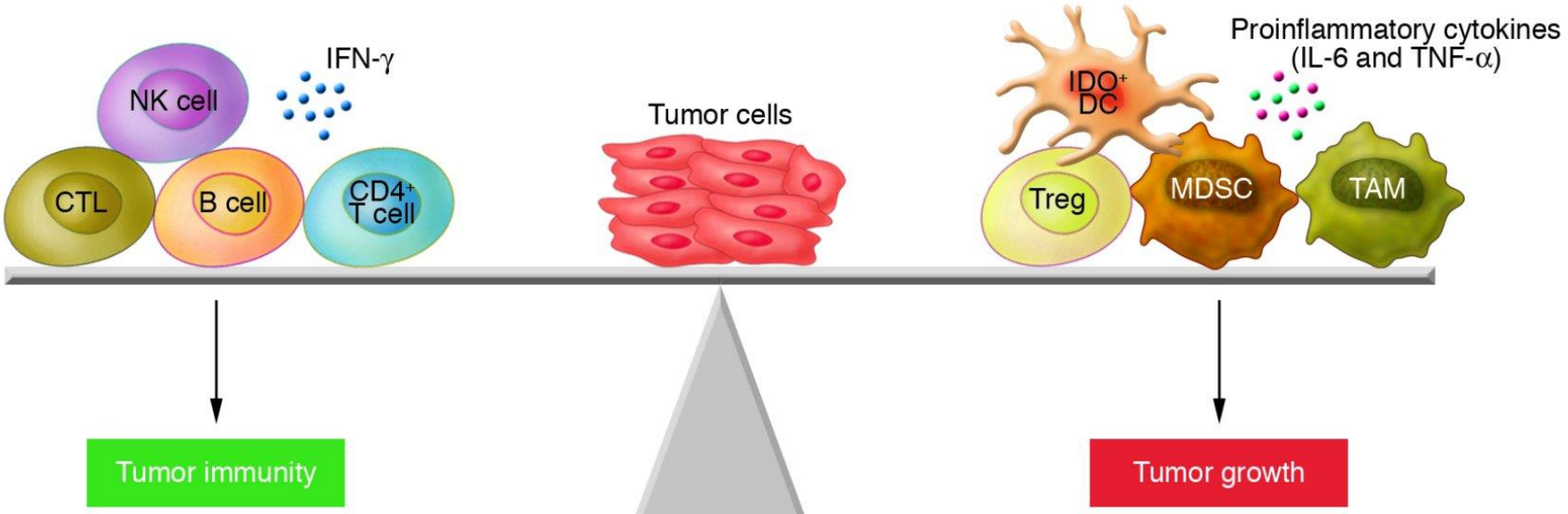
$CD45RO_{CT}CD45RO_{IM}$ evaluation



Galon et al, Science 313: 5795 (2006)

How does immunity increase survival yet so infrequently lead to cure?

- Mutational evolution of tumor cells to avoid the immune response
- Evolution of the response from acute inflammatory to chronic / wound healing
- Intrinsic cellular suppression of the response

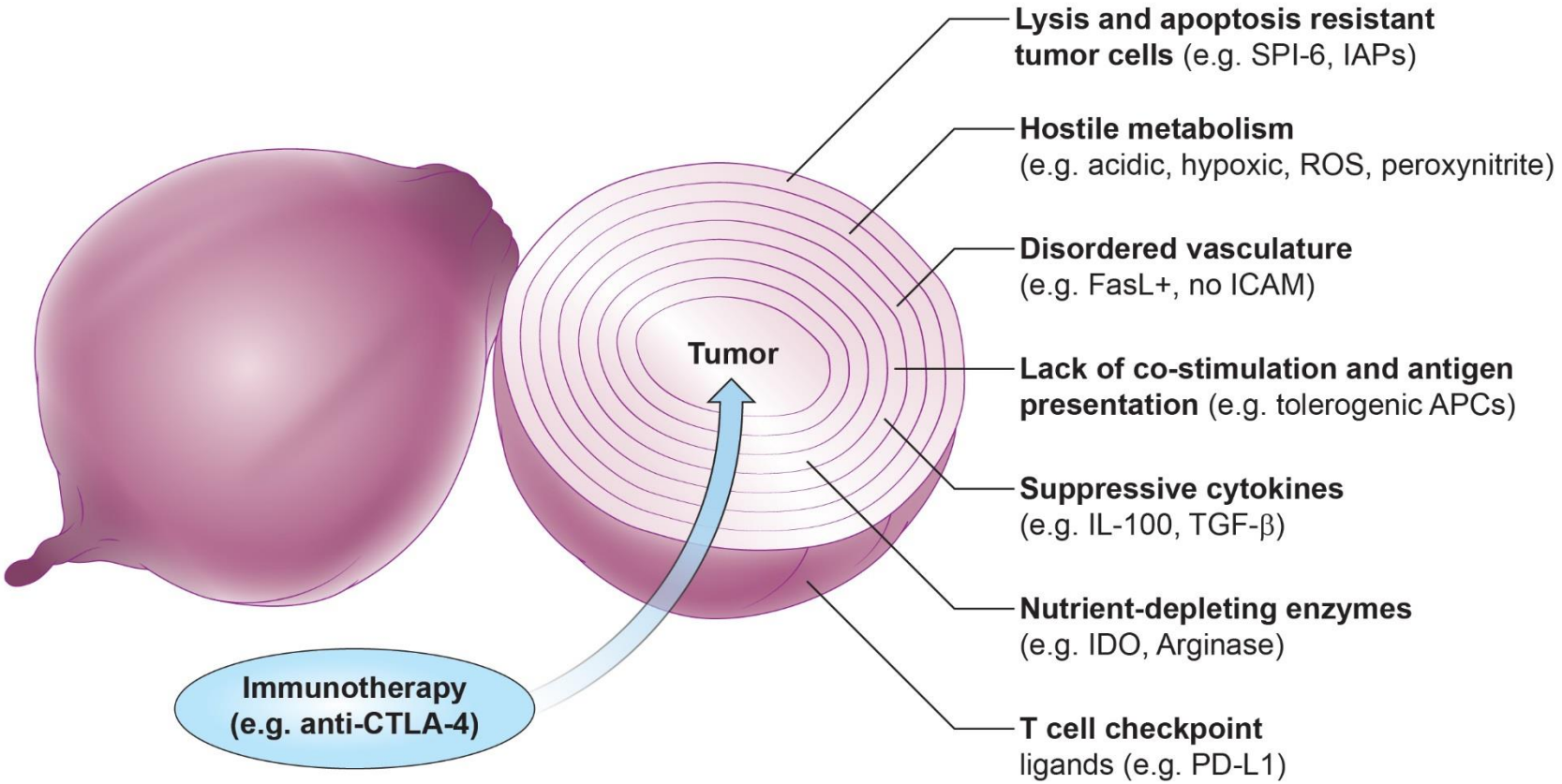


Acute inflammatory response
Typical for pathogens

Type II inflammatory response
Typical for wound healing

Modified from Bhardwaj, J Clin Invest. 117:1130(2007)

Multi-layered immunosuppression



- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor

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To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of immunotherapy, then, is to restore the capacity of the immune system to recognize and reject cancer.