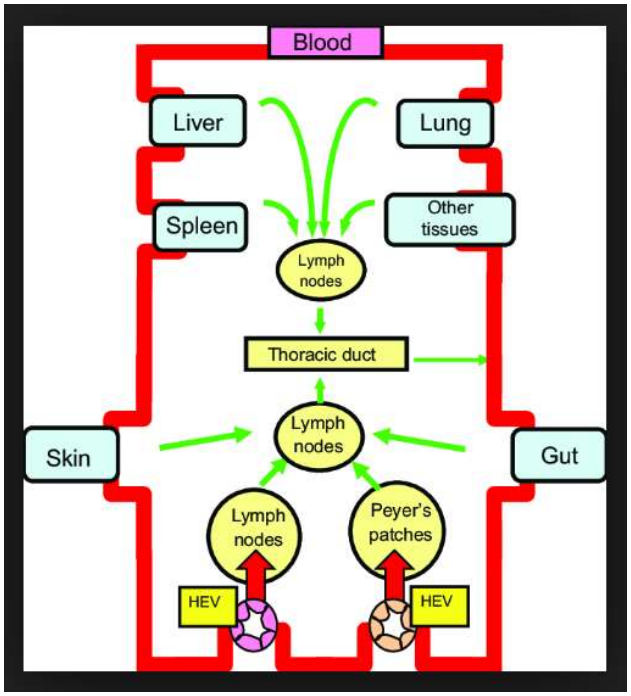


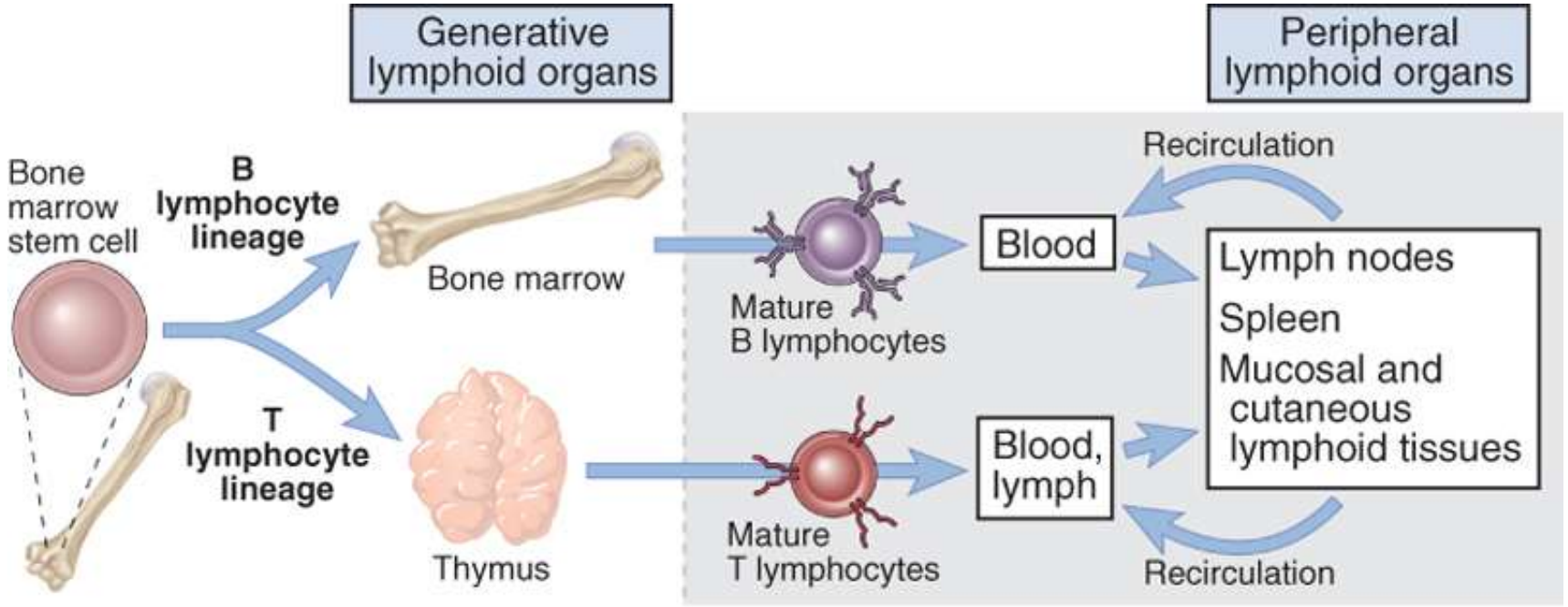
RECLUTAMENTO DEI LEUCOCITI NEI TESSUTI: MIGRAZIONE E RICIRCOLAZIONE DELLE CELLULE DEL DEL SISTEMA IMMUNITARIO

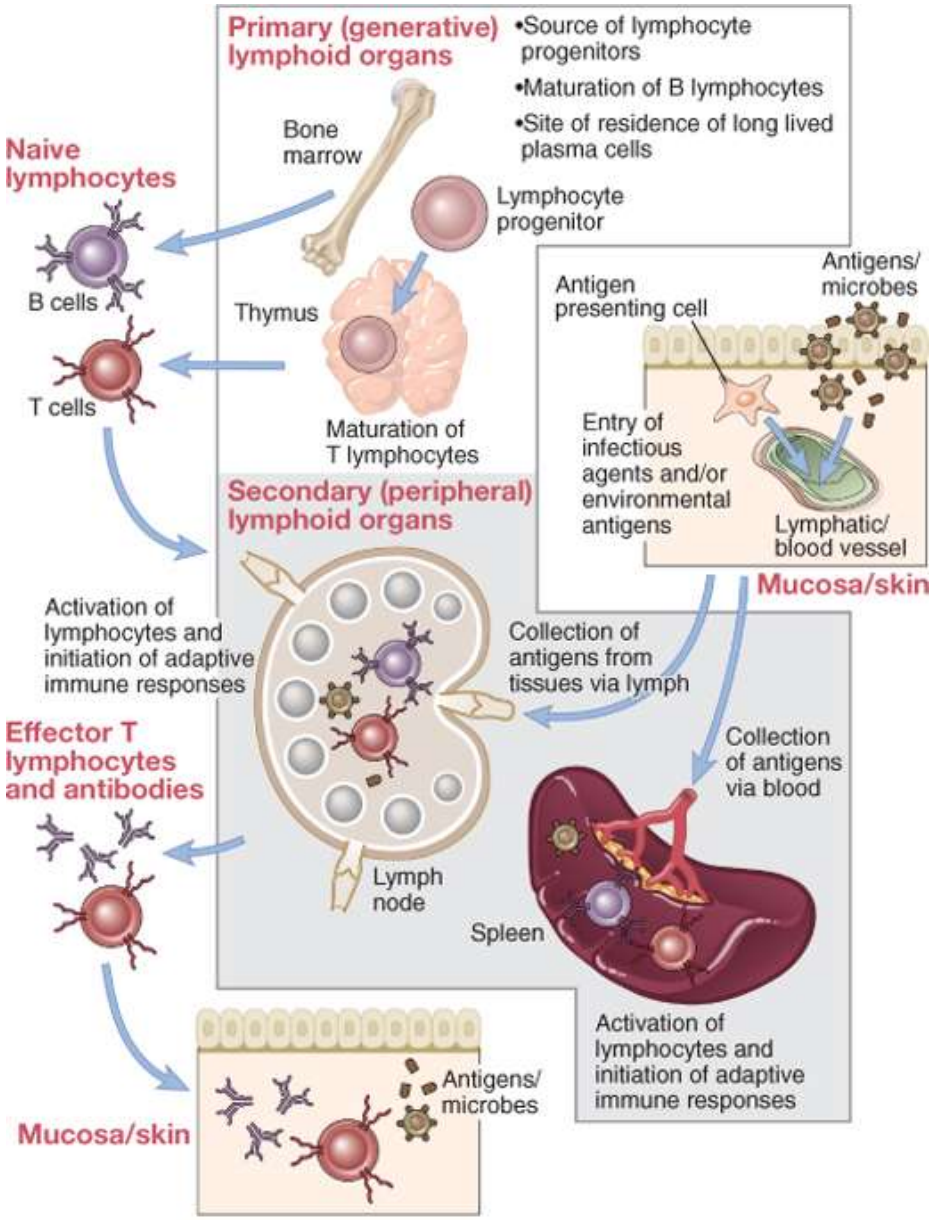
15 e 16 Aprile 2025

Una delle caratteristiche peculiari del SI è il movimento costante e strettamente regolato delle sue componenti cellulari che possono passare dal sangue ai tessuti e spesso ritornare in circolo.
Questo movimento assolve a 3 funzioni principali:

1. Indirizzamento delle cellule mieloidi (neutrofili e monociti) dal sangue ai focolai tissutali di infezione
2. Indirizzamento dei linfociti dai siti di maturazione (timo e midollo osseo) agli organi linfoidi secondari
3. Indirizzamento dei linfociti effettori dagli organi linfoidi secondari (sede di attivazione) ai siti di infezione

La migrazione di un leucocita dal sangue ad un determinato tessuto o verso un sito di infezione o di danno tissutale viene definita HOMING leucocitario mentre il movimento dei leucociti dal sangue ai tessuti viene definito MIGRAZIONE o RECLUTAMENTO.
La capacità dei linfociti di migrare ripetutamente in organi linfoidi secondari , risiedervi in via transitoria e tornare al sangue viene definita RICIRCOLAZIONE.





Molecole di adesione espresse dai leucociti e dalle cellule endoteliali coinvolte nel reclutamento leucocitario

L'adesione dei leucociti circolanti all'endotelio vascolare è mediato da 2 classi di molecole:

- ***SELECTINE***
- ***INTEGRINE***

e dai loro ligandi.

L'espressione di queste molecole varia tra le diverse popolazioni leucocitarie e nei vasi sanguigni presenti nei diversi distretti anatomici.

Selectine: molecole di adesione che legano carboidrati sulla membrana plasmatica; mediano lo step iniziale a bassa affinità di adesione all'endotelio delle venule post-capillari. Il dominio extracellulare è simile alle lectine di tipo C.

Integrine: molecole di superficie che mediano l'adesione cellula-cellula o cellula-matrice extracellulare. Sono tutti eterodimeri (catena α e catena β). Oltre alla funzione di molecole di adesione, sono anche in grado di trasdurre il segnale.

TABLE 3.1 Major Leukocyte-Endothelial Adhesion Molecules

Family	Molecule	Distribution	Ligand (Molecule; Cell Type)
Selec		Endothelium activated by histamine or thrombin	Sialyl Lewis X on PSGL-1 and other glycoproteins; neutrophils, mon… memory)
		Endothelium activated by cytokines (TNF, IL-1)	Sialyl Lewis X (e.g., … neutrophils, monocytes, T cells (effector, memory)
		Neutrophils, monocytes, T cells (naive … B cells (naive)	Sialyl Lewis X/PNAd on GlyCAM-1, CD34, MadCAM-1, others; endothelium (HEV)
Integrin	LFA-1 (CD11aCD18)	Neutrophils, monocytes, T cells (naive, effector, memory), B cells (naive)	ICAM-1 (CD54), ICAM-2 (CD102); endothelium (upregulated when cytokine activated)
	Mac-1 (CD11bCD18)	Neutrophils, monocytes, dendritic cells	ICAM-1 (CD54), ICAM-2 (CD102); endothelium (upregulated when cytokine activated)
	VLA-4 (CD49aCD29)	Monocytes, T cells (naive, effector, memory)	VCAM-1 (CD106); endothelium (upregulated when cytokine activated)
	$\alpha_4\beta_7$ (CD49dCD29)	Monocytes, T cells (gut homing, naive, effector, memory), B cells (gut homing)	VCAM-1 (CD106), MadCAM-1; endothelium in gut and gut-associated lymphoid tissues

Stoccate nei granuli citoplasm. delle cellule endoteliali ed espresse sulla superficie nell'arco di 1-2 ore , dopo stimolazione con citochine o dal rilascio di istamina o trombina

Cruciale per indirizzare i In T e B ai In attreverso HEV

I leucociti esprimono molecole che legano la E la la P-selectina

CLA-1, Cutaneous lymphocyte antigen 1; *GlyCAM-1,* glycan-bearing cell adhesion molecule 1; *HEV,* high endothelial venule; *ICAM-1,* intracellular adhesion molecule 1; *IL-1,* interleukin-1; *LFA-1,* leukocyte function–associated antigen 1; *MadCAM-1,* mucosal addressin cell adhesion molecule 1; *PNAd,* peripheral node addressin; *PSGL-1,* P-selectin glycoprotein ligand 1; *TNF,* tumor necrosis factor; *VCAM-1,* vascular cell adhesion molecule 1; *VLA-4,* very late antigen 4.

Le integrine sono proteine di membrana responsabili dell'adesione intercellulare o delle cellule alla matrice extracellulare.
Sono costituite da eterodimeri tra una catena α e una β

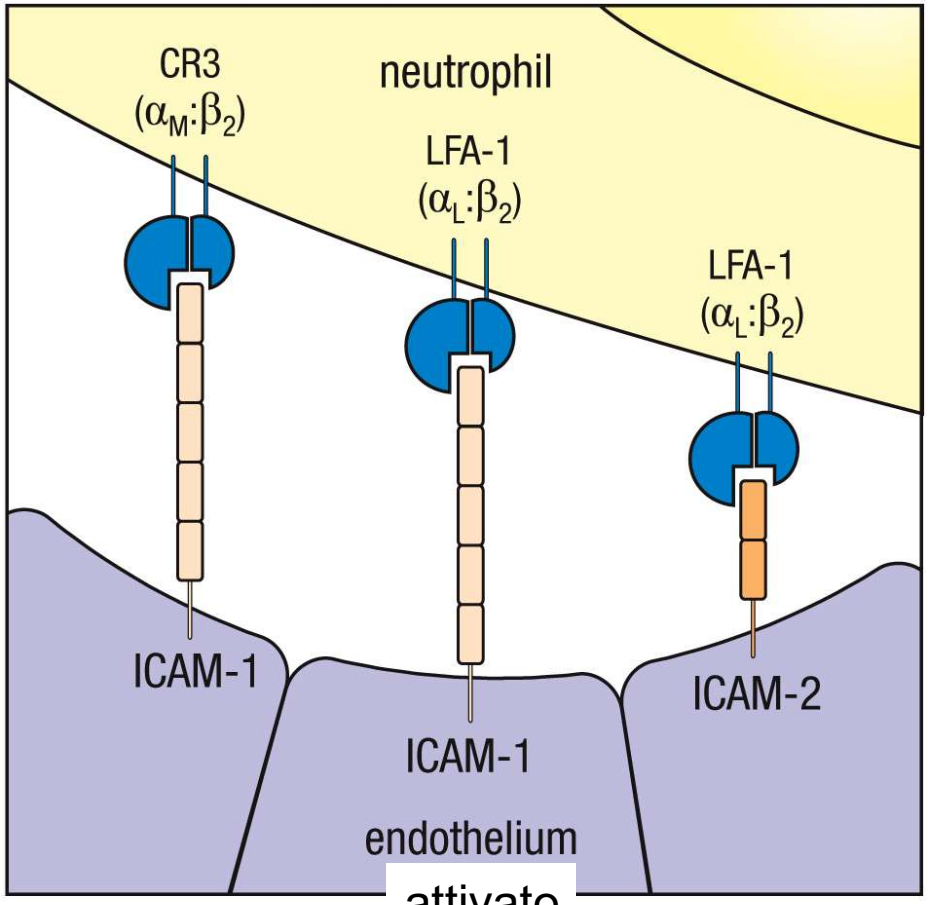


Figure 3.30 Janeway's Immunobiology, 9th ed. (© Garlar

Ligandi di LFA-1:
ICAM-1
ICAM-2
ICAM-3

Selectins, integrins, addressins, CAMs

Cell-adhesion molecules (CAM) control interactions between leukocytes and endothelial cells during an inflammatory response.

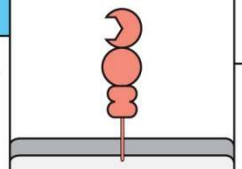
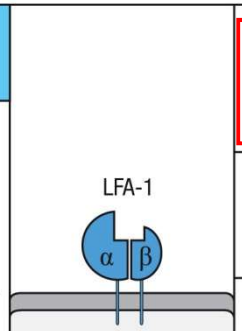
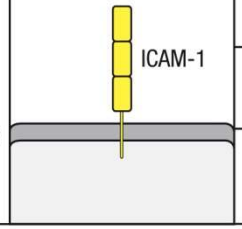
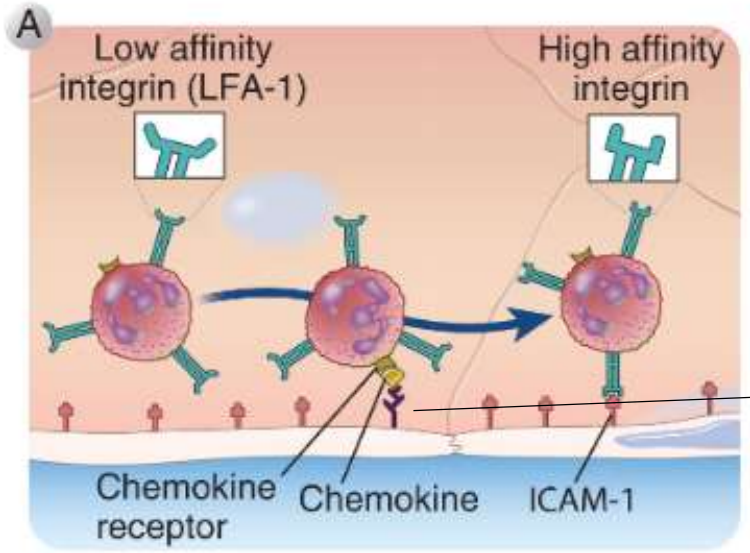
		Name	Tissue distribution	Ligand
Selectins Bind carbohydrates. Initiate leukocyte–endothelial interaction		P-selectin (PADGEM, CD62P)	Activated endothelium and platelets	PSGL-1, sialyl-Lewis^x
		E-selectin (ELAM-1, CD62E)	Activated endothelium	Sialyl-Lewis^x
Integrins Bind to cell-adhesion molecules and extracellular matrix. Strong adhesion		α_L:β_2 (LFA-1, CD11a:CD18)	Monocytes, T cells, macrophages, neutrophils, dendritic cells, NK cells	ICAM-1, ICAM-2
		α_M:β_2 (CR3, Mac-1, CD11b:CD18)	Neutrophils, monocytes, macrophages, NK cells	ICAM-1, iC3b, fibrinogen
		α_X:β_2 (CR4, p150.95, CD11c:CD18)	Dendritic cells, macrophages, neutrophils, NK cells	iC3b
		α_5:β_1 (VLA-5, CD49d:CD29)	Monocytes, macrophages	Fibronectin
Immunoglobulin superfamily Various roles in cell adhesion. Ligand for integrins		ICAM-1 (CD54)	Activated endothelium, activated leukocytes	LFA-1, Mac1
		ICAM-2 (CD102)	Resting endothelium, dendritic cells	LFA-1
		VCAM-1 (CD106)	Activated endothelium	VLA-4
		PECAM (CD31)	Activated leukocytes, endothelial cell–cell junctions	CD31

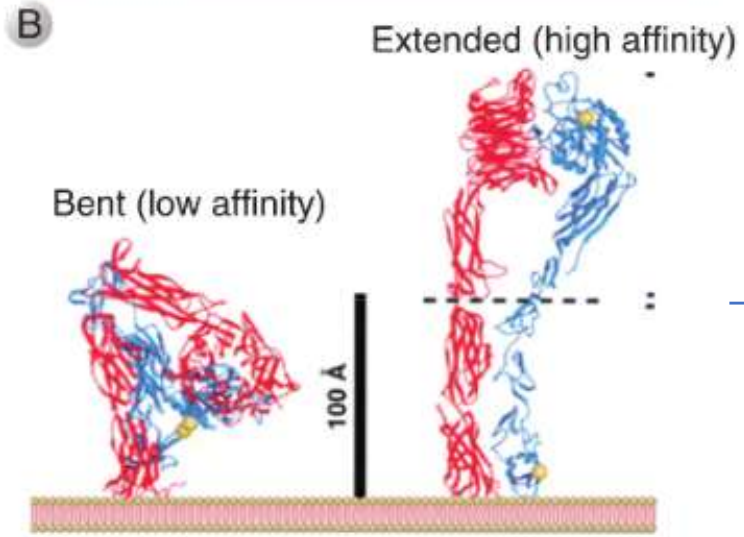
Figure 3.29 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Le integrine aumentano rapidamente la loro affinità in risposta a segnali attivati dal legame delle chemochine ai rispettivi recettori

Le integrine sono espresse sui leuciti circolanti in uno stato di bassa affinità. Quando un leucocita entra in contatto con le cellule endoteliali attivate, le chemochine presenti sulla superficie vengono riconosciute da specifici recettori.



Le chemochine prodotte nel tessuto si legano ai proteoglicani Eparan solfato sulle cellule endoteliali



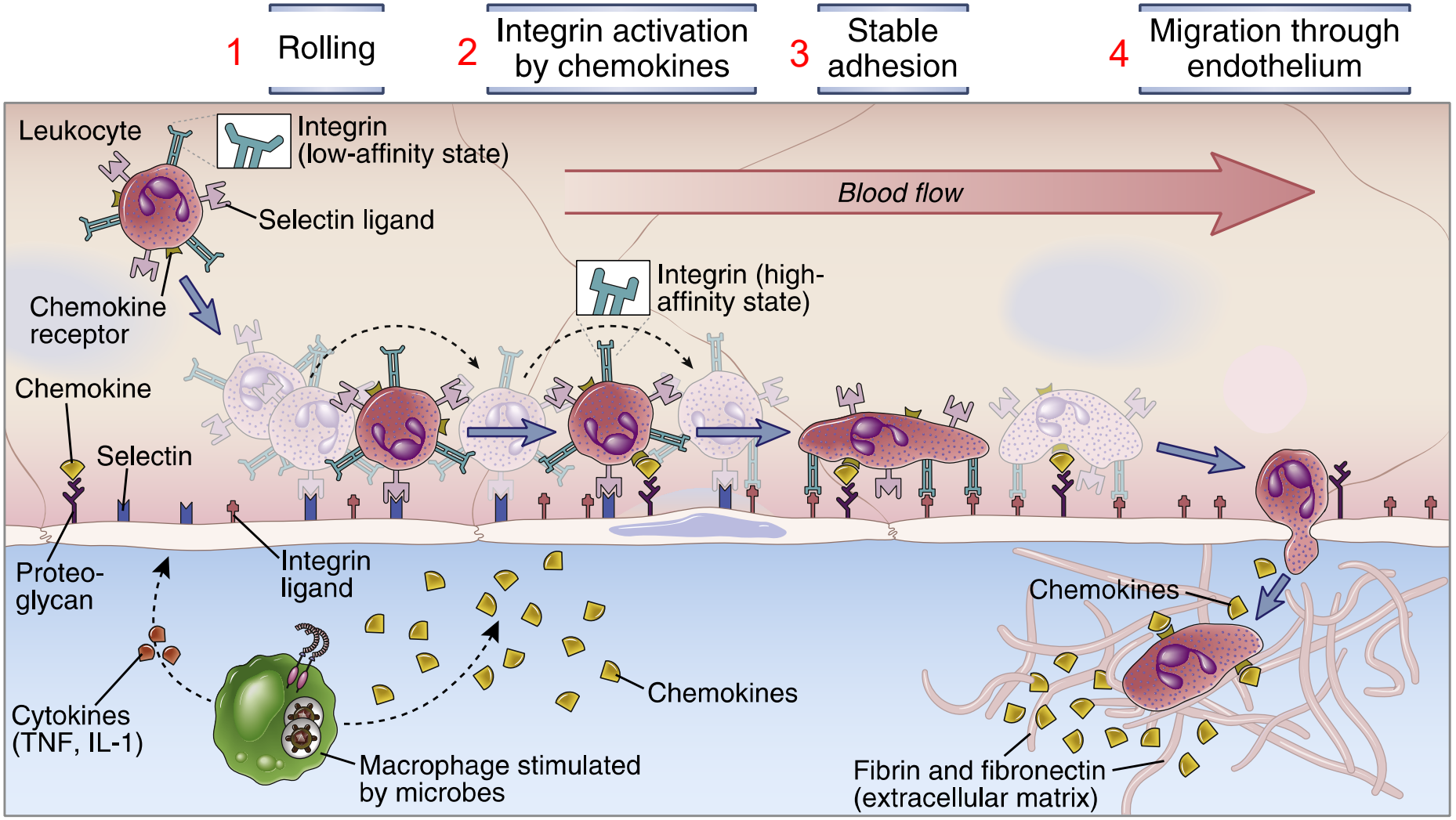
Inside-out signaling

Interazione leucociti-endotelio e reclutamento dei leucociti nei tessuti

- Il reclutamento dal sangue ai tessuti necessita l'adesione ed il passaggio dei leucociti all'endotelio delle venule postcapillari ed il passaggio nella regione extravascolare.

- Questo processo avviene attraverso tappe sequenziali orchestrate da specifiche molecole di adesione e chemochine

Ruolo delle molecole di adesione nella migrazione leucocitaria



Abbas 9th ed 2018

Neutrophils make up the first wave of cells that cross the blood vessel wall to enter an inflamed tissue

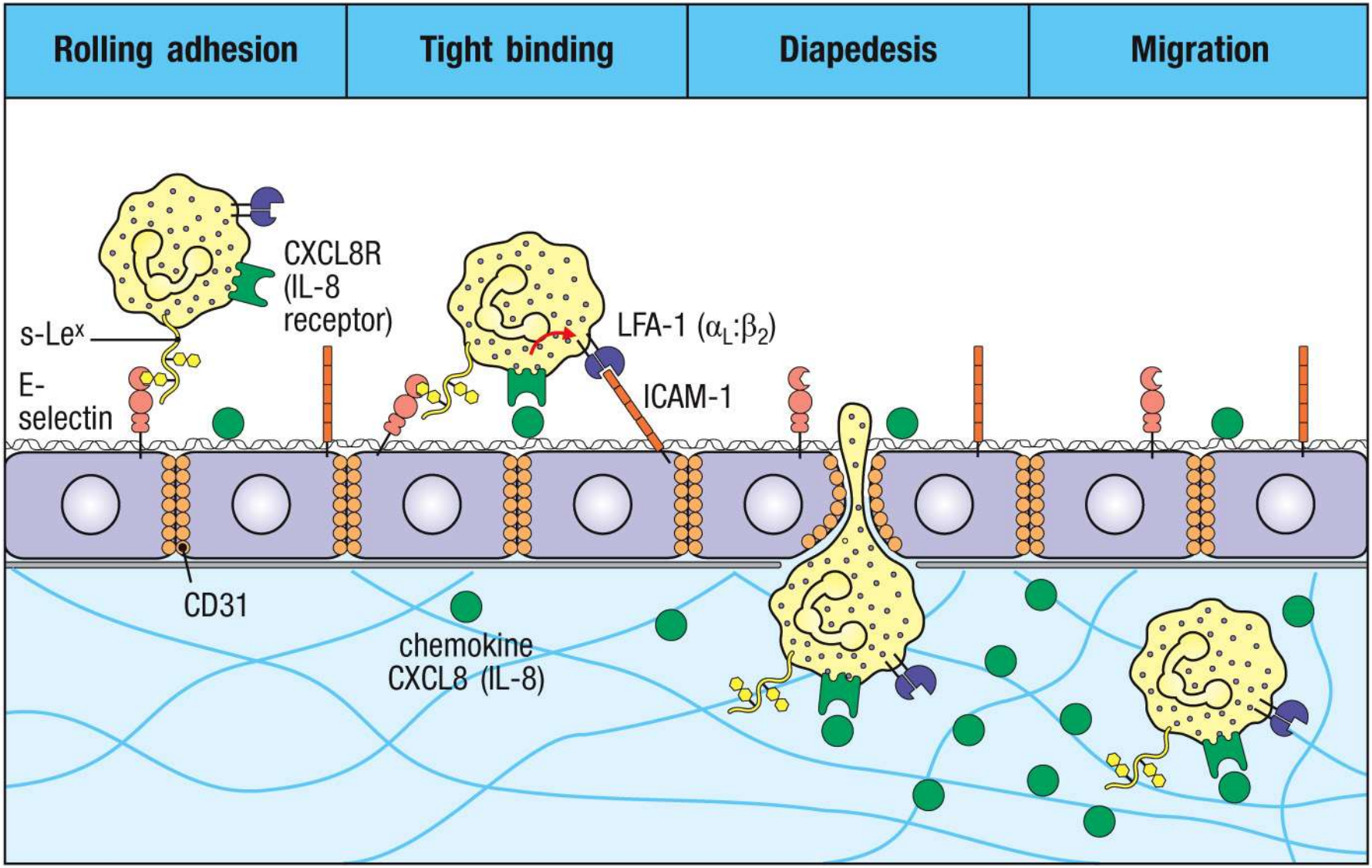
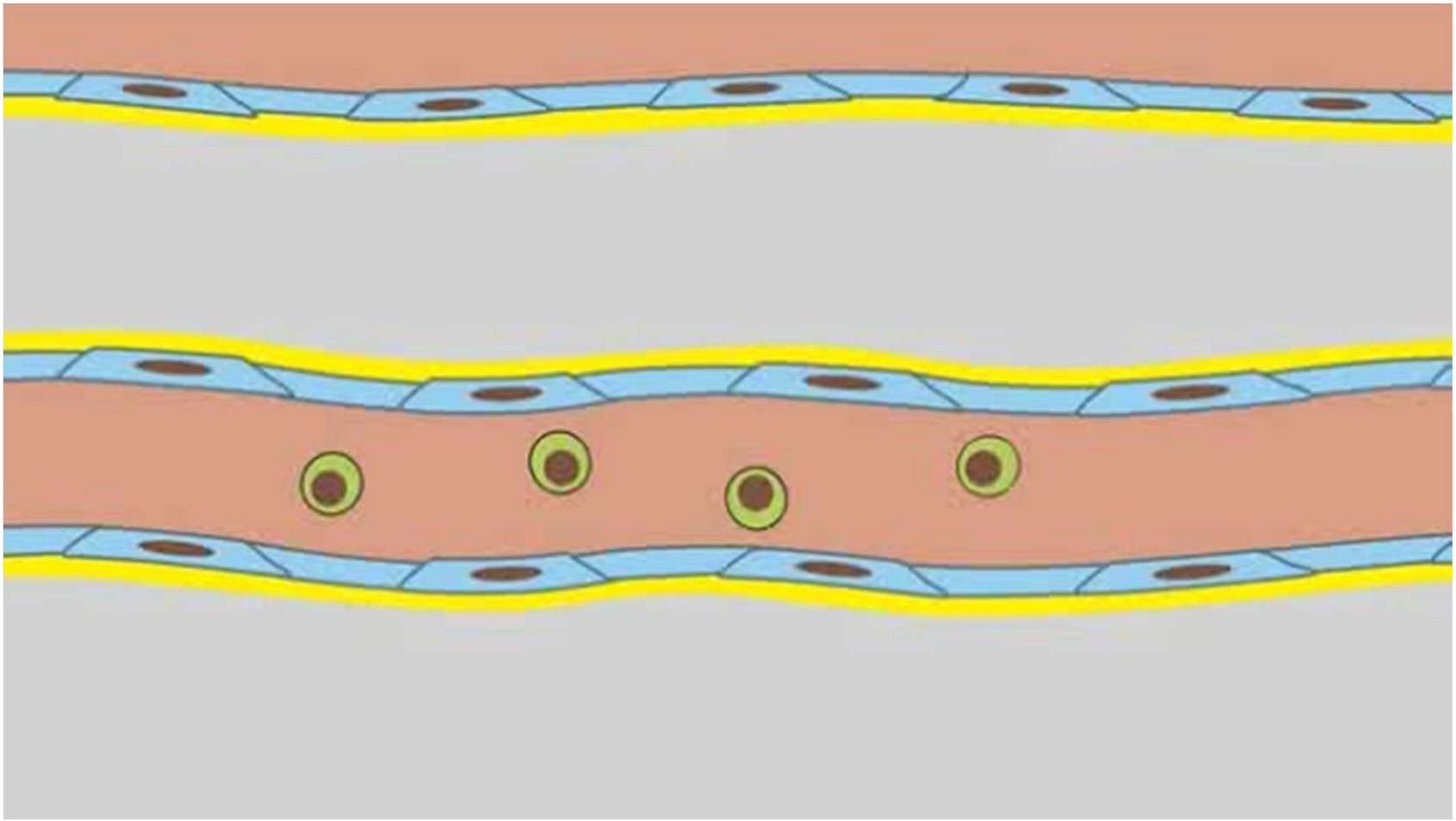
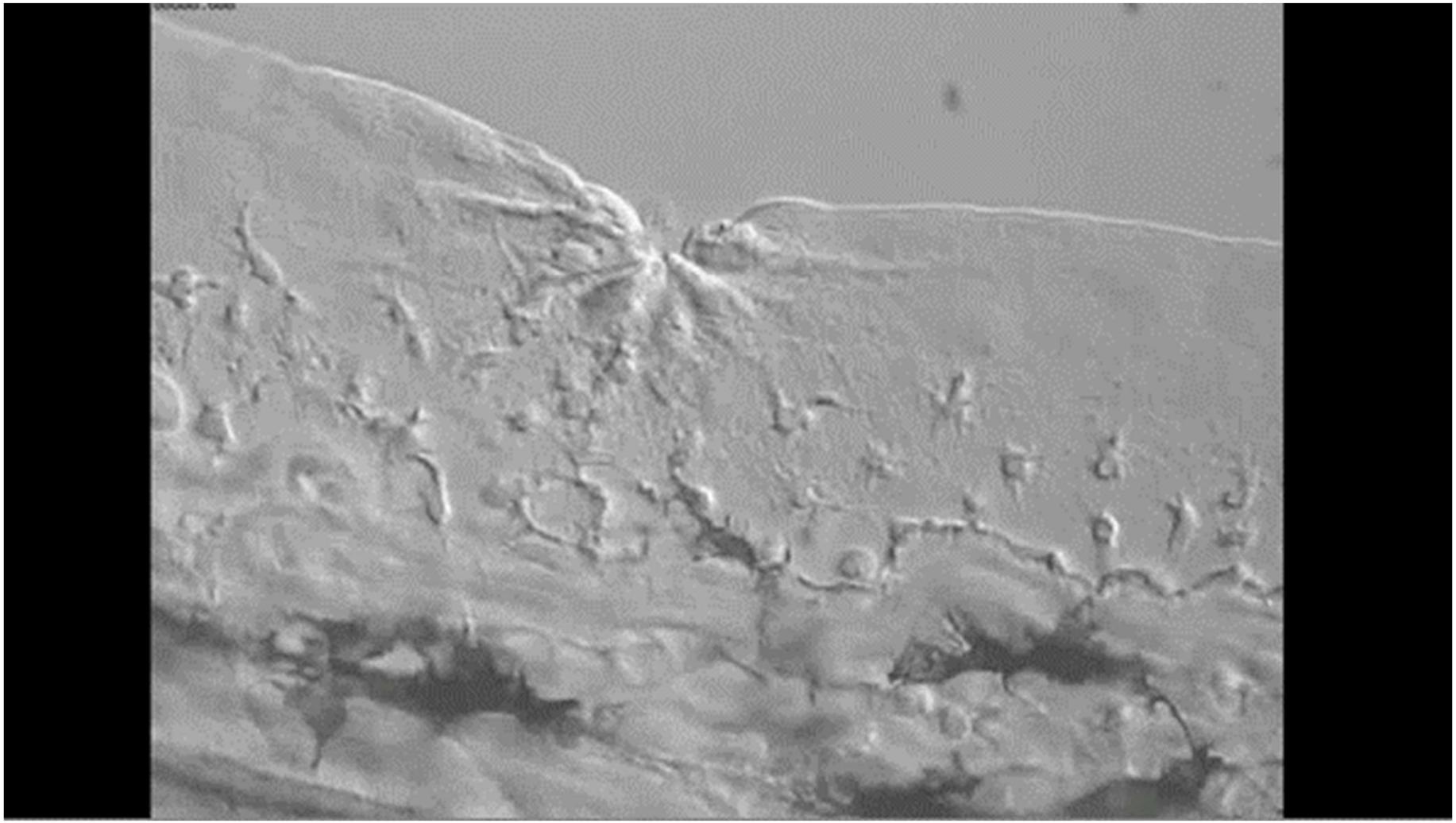


Figure 3.31 (part 2 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

LEUKOCYTE ROLLING



Lymphocyte homing



MIGRAZIONE E RICIRCOLAZIONE DEI LINFOCITI T

- LINFOCITI T NAIVE (ricircolazione linfocitaria tra sangue e organi linfoidi secondari; homing e HEV).
- LINFOCITI T EFFETTORI (verso i siti di infiammazione)
- LINFOCITI T DI MEMORIA

NK cells distinguish infected and stressed cells from healthy cells.

NK cell mediated killing is a function of **inhibitory and activating signals** received by NK cell receptors from ligands on the target cell.

NK cell activating receptors trigger cell killing.
NK inhibitory receptors prevent cell killing.

Usually engagement of an inhibitory receptor will prevent killing by an engaged activating receptor.

NK cells recognize their target cells via a system of **germline-encoded activating and inhibitory receptors** that recognize membrane-bound ligands on potential target cells

NK cells express activating and inhibitory receptors to distinguish between healthy and infected cells

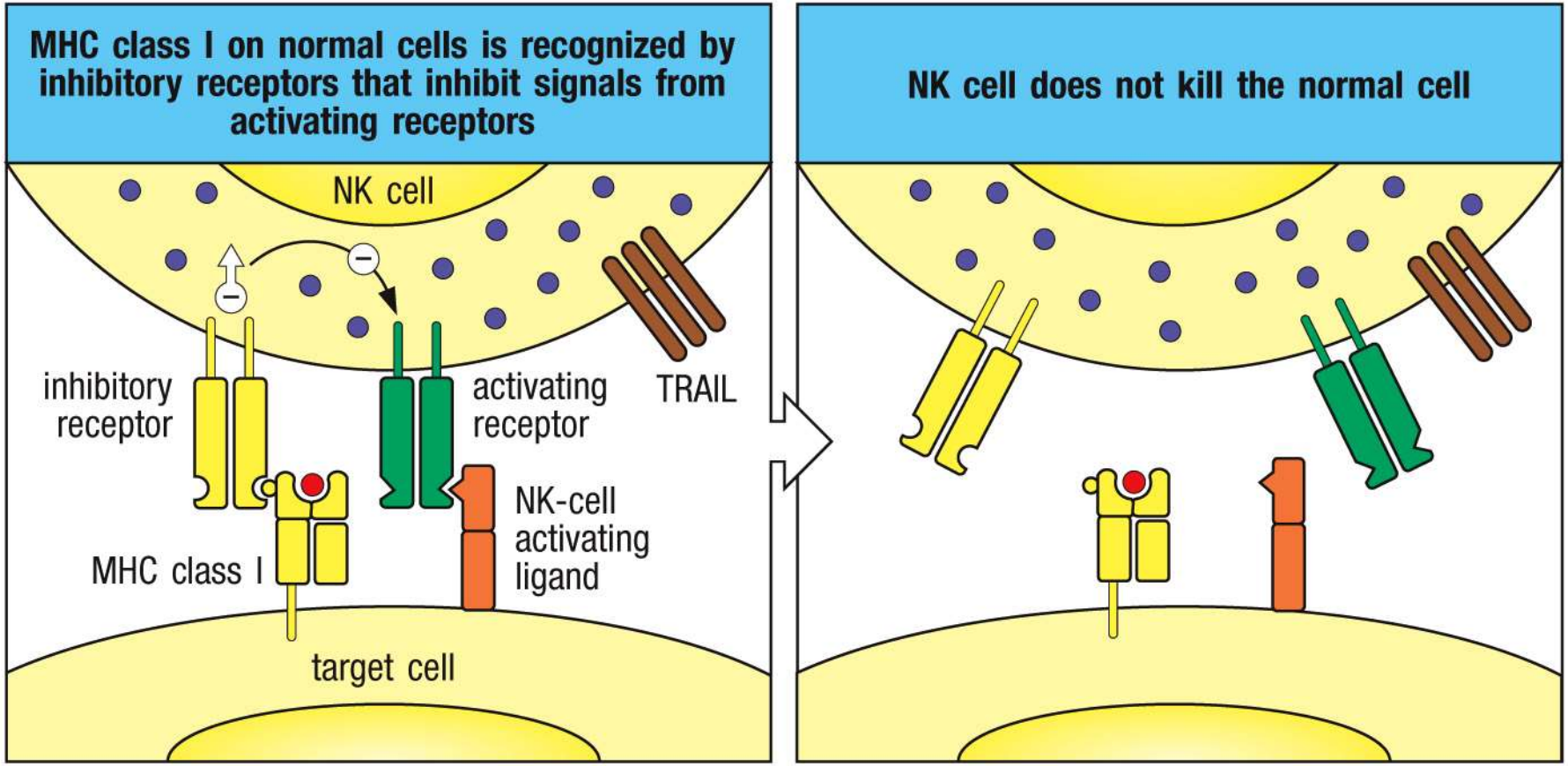


Figure 3.39 (part 1 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

NK cells express activating and inhibitory receptors to distinguish between healthy and infected cells

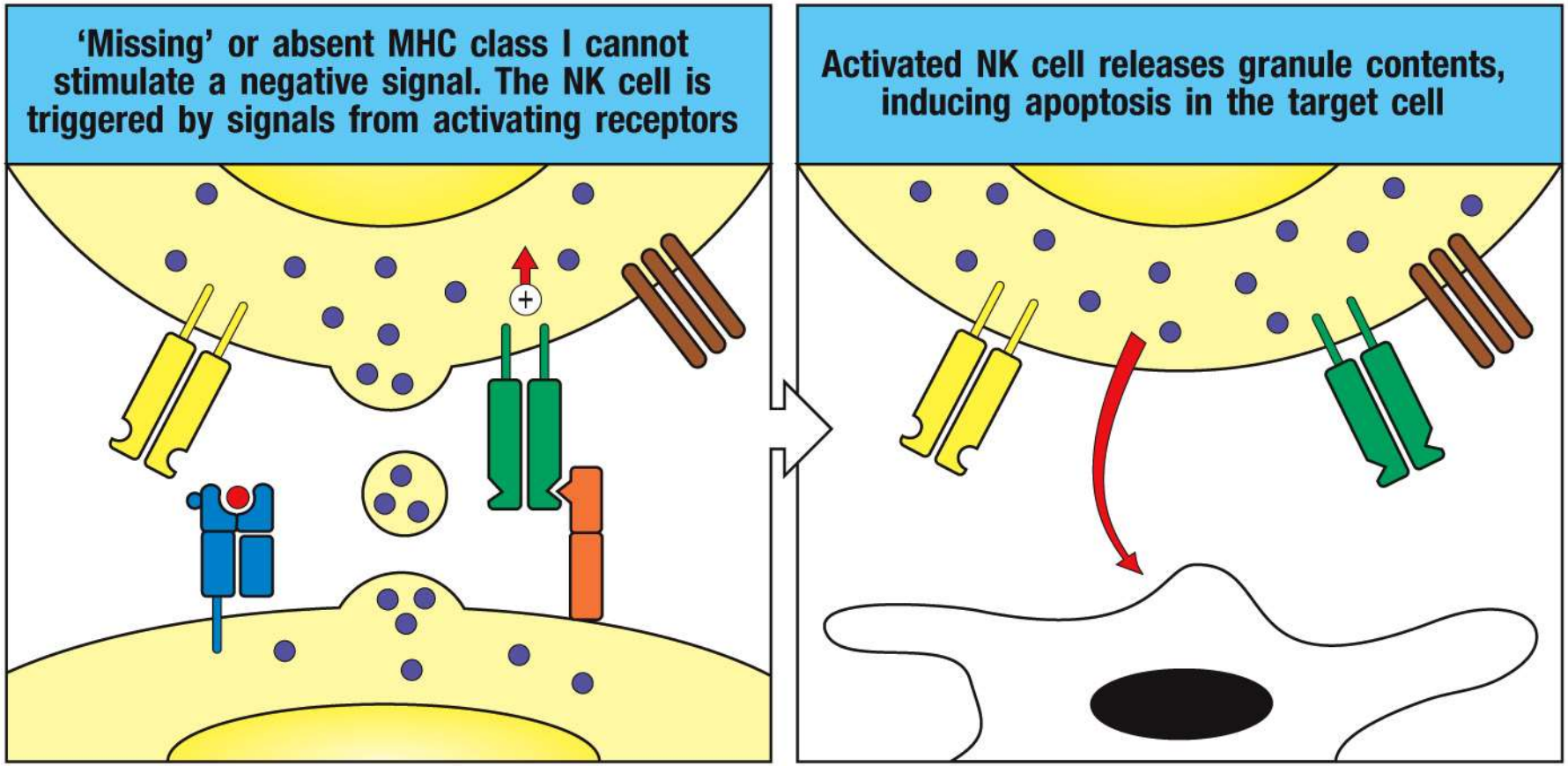


Figure 3.39 (part 2 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

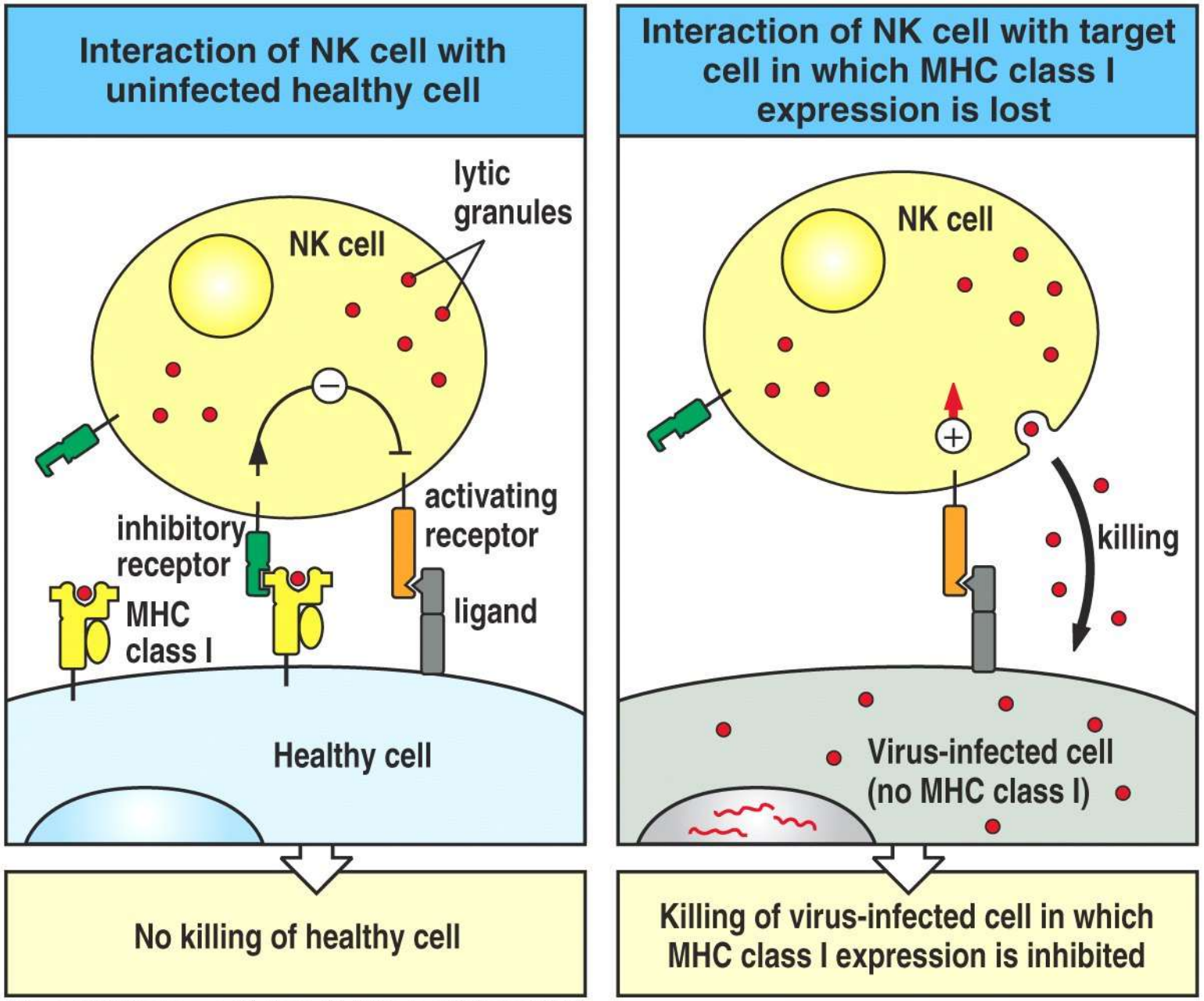
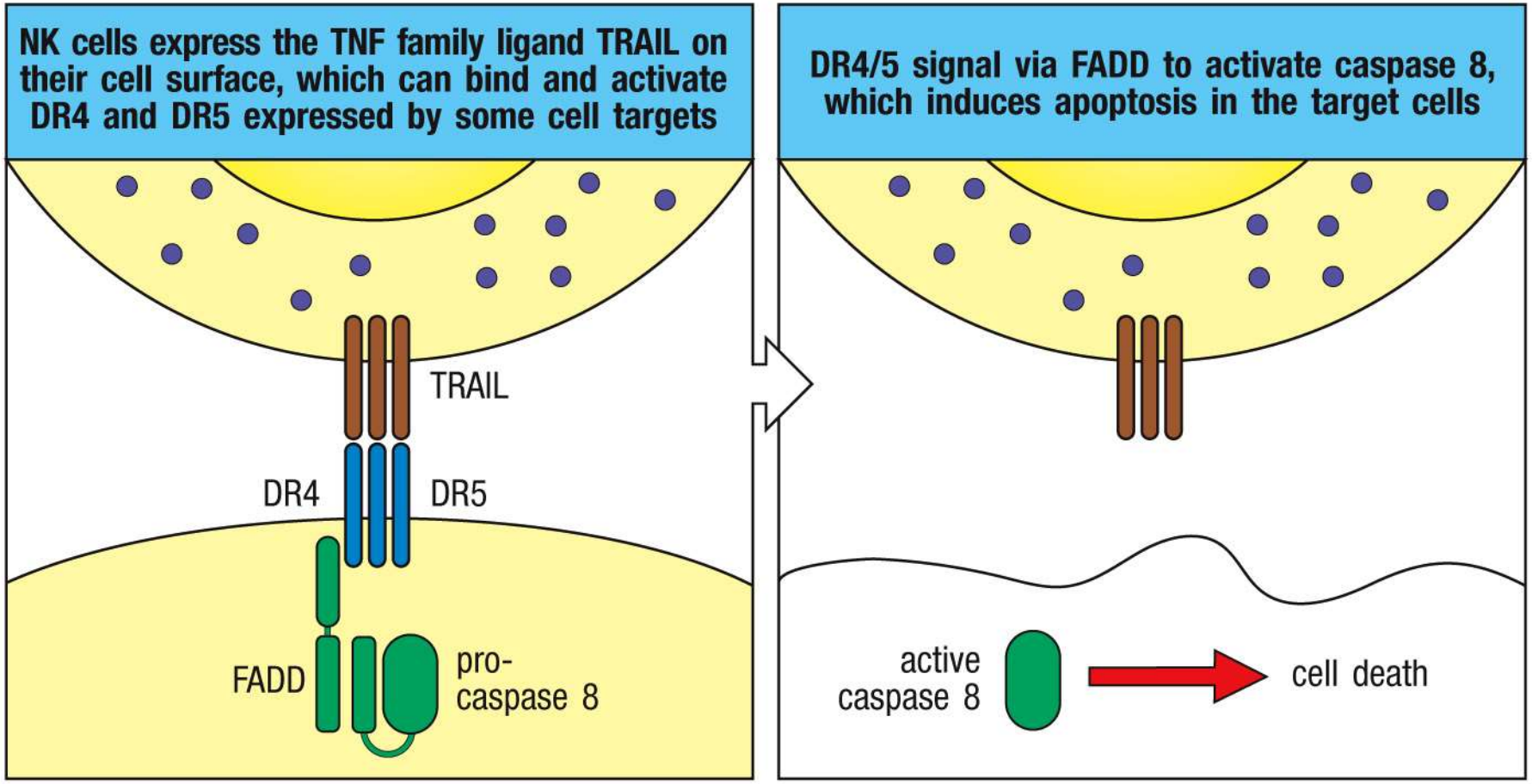


Figure 8-32 The Immune System, 2/e (© Garland Science 2005)

NK cells express activating and inhibitory receptors to distinguish between healthy and infected cells



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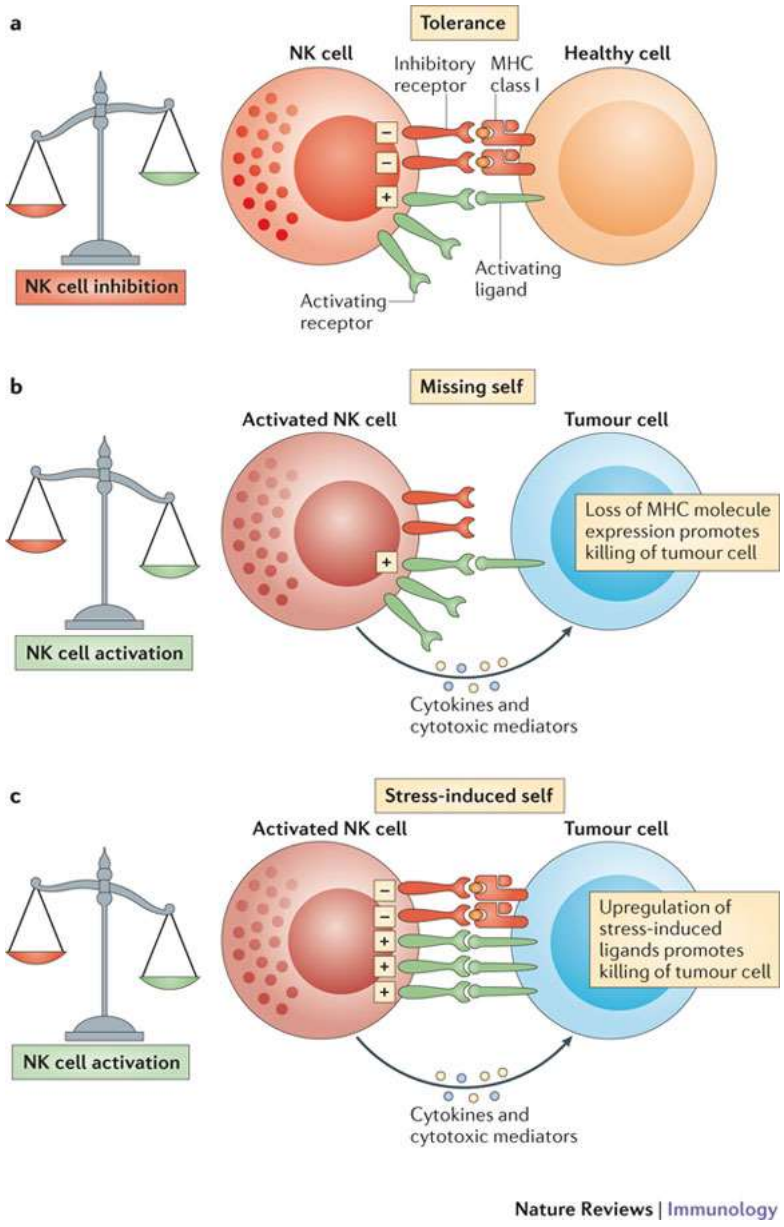
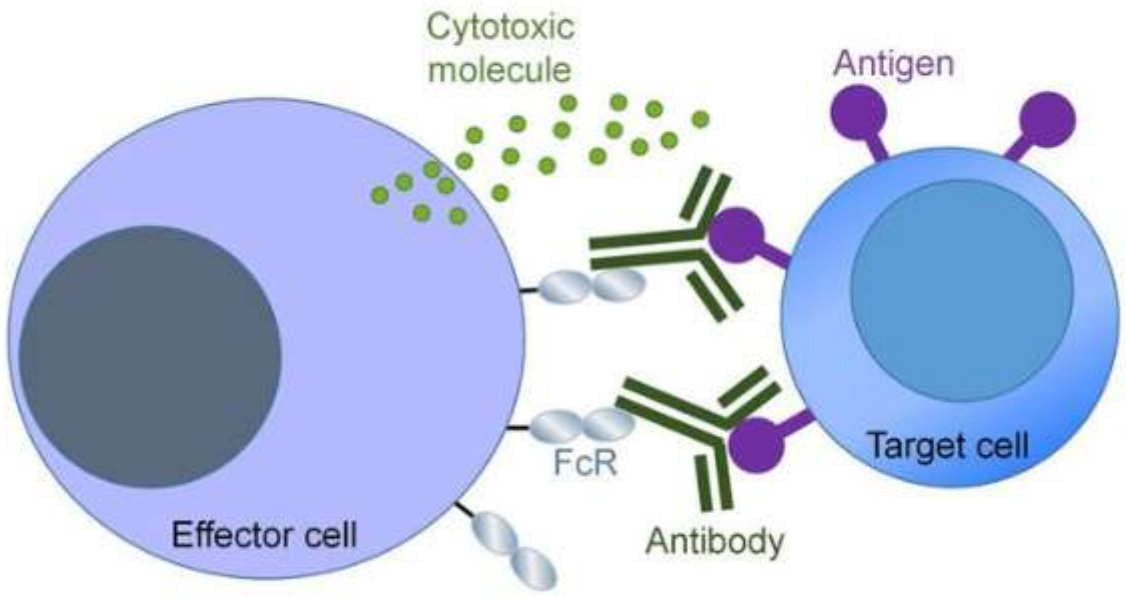
Recognition of tumour cells by NK cells.



a | Natural killer (NK) cells are tolerant to healthy host cells, as the strength of the activating signals they receive on encountering these cells is dampened by the engagement of inhibitory receptors (tolerance). b | Tumour cells may lose expression of MHC class I molecules. NK cells become activated in response to these cells, as they are no longer held in check by the inhibitory signal delivered by MHC class I molecule engagement. This is known as 'missing-self' triggering of NK cell activation. c | In addition, NK cells are selectively activated by 'stressed' cells, which upregulate activating ligands for NK cells and thereby overcome the inhibitory signalling delivered by MHC class I molecules. This is known as 'stress-induced self' triggering of NK cell activation. In both conditions, NK cell activation leads to tumour elimination directly (through NK cell-mediated cytotoxicity) or indirectly (through the production of pro-inflammatory cytokines, such as interferon-γ).

Antibody-dependent cellular cytotoxicity (ADCC)



ADCC is triggered when the Fab domain of an antibody binds to an antigen on the target cell and the Fc domain of the same antibody molecule binds to the FcR on the effector cell.