Entzündungsreaktionen und die Entstehung adaptiver Immunantworten

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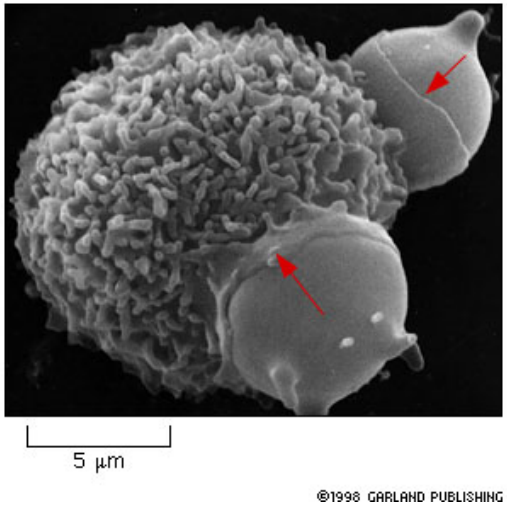
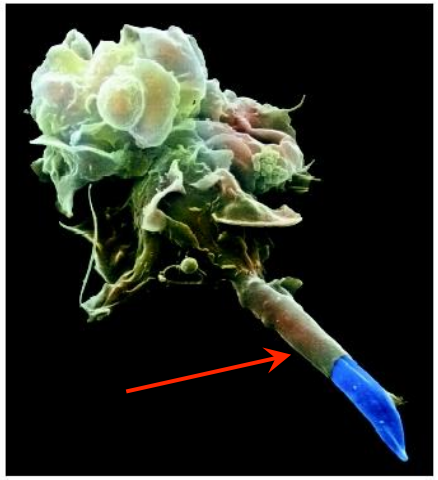
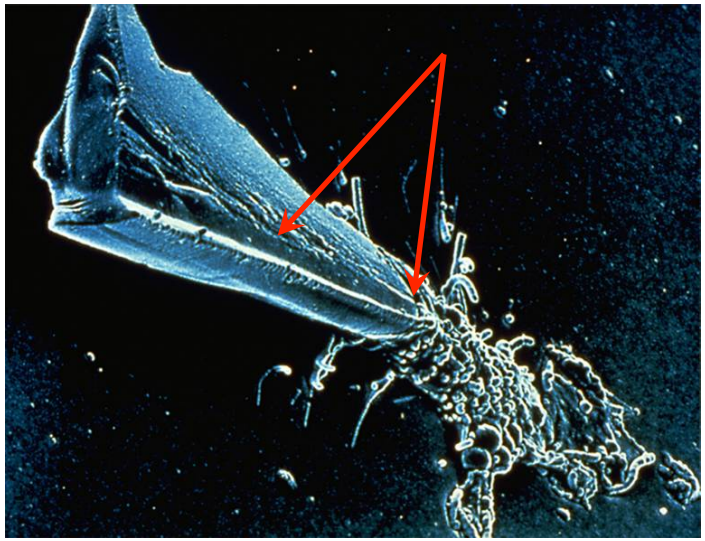
Komponenten des angeborenen Immunsystems

- Externe Barrieren (mechanisch, chemisch, mikrobiell)
- Lösliche Faktoren (teils „pattern recognition receptors“):
  - Kationische antimikrobielle Peptide
  - „Natürliche“ Antikörper
  - Komplementsystem
  - Typ I Interferone
- „Wächterzellen“:
  Makrophagen, Mastzellen, Natürliche Killer (NK)-Zellen, Dendritische Zellen
- „Effektorzellen“:
  Neutrophile Granulocyten, Makrophagen, Natürliche Killer (NK)-Zellen

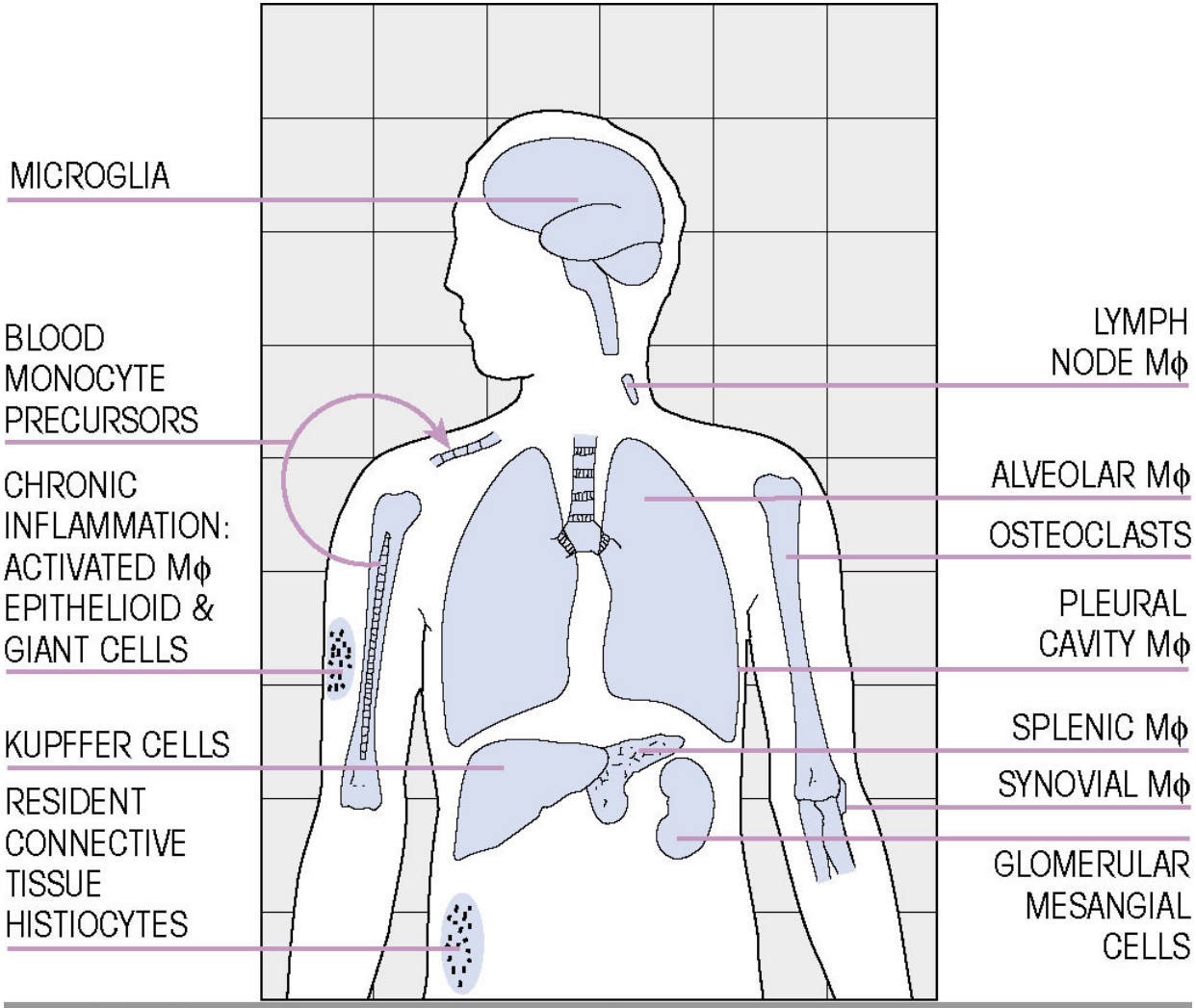
Professionelle Freßzellen: Makrophagen und Mikrophagen (Neutrophile Granulocyten)







Makrophagen/Monocyten:
Bestandteil des Retikuloendothelialen/-histiocytären Systems



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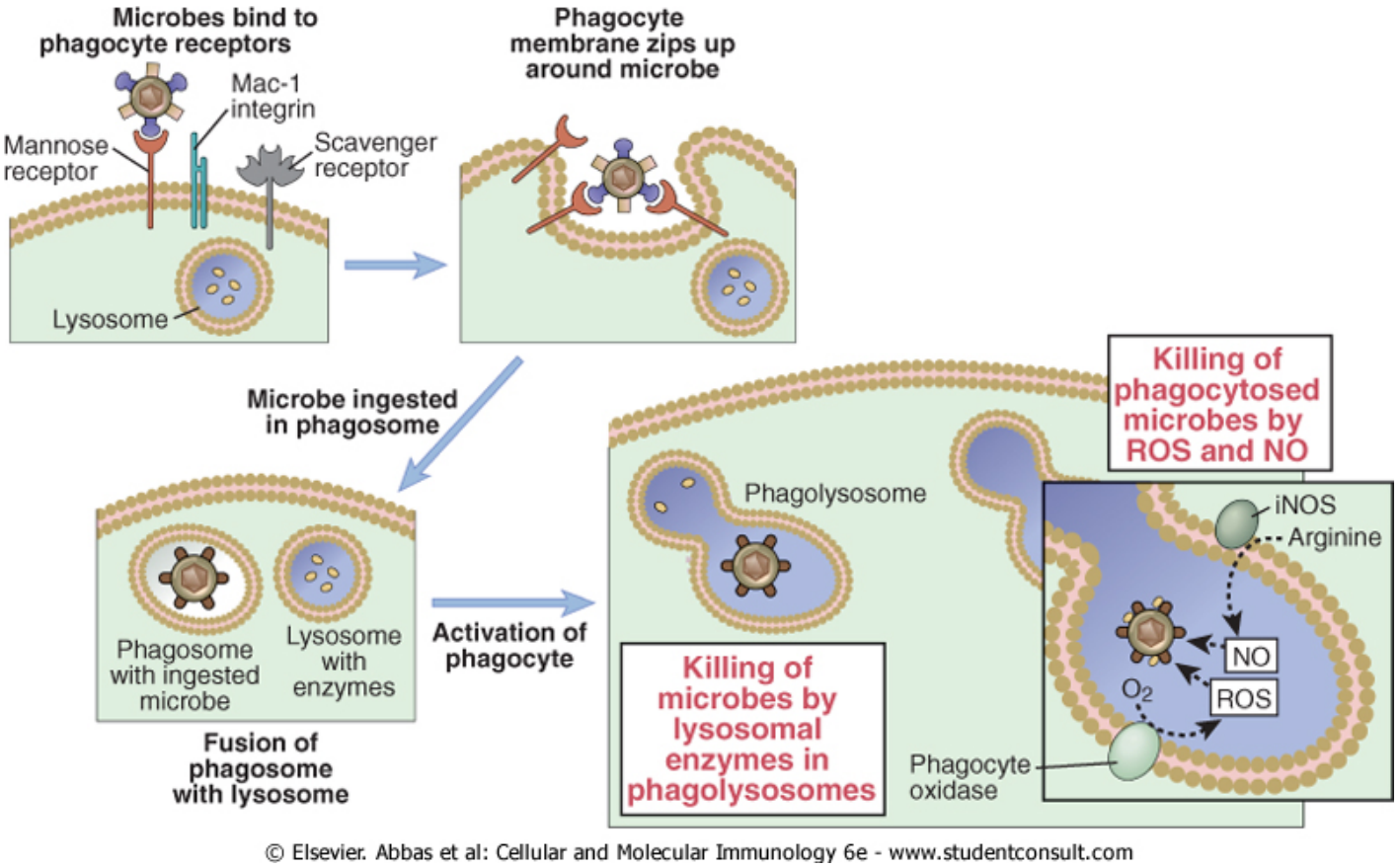
Phagocyten: Makrophagen und Neutrophile Granulocyten („Mikrophagen“)



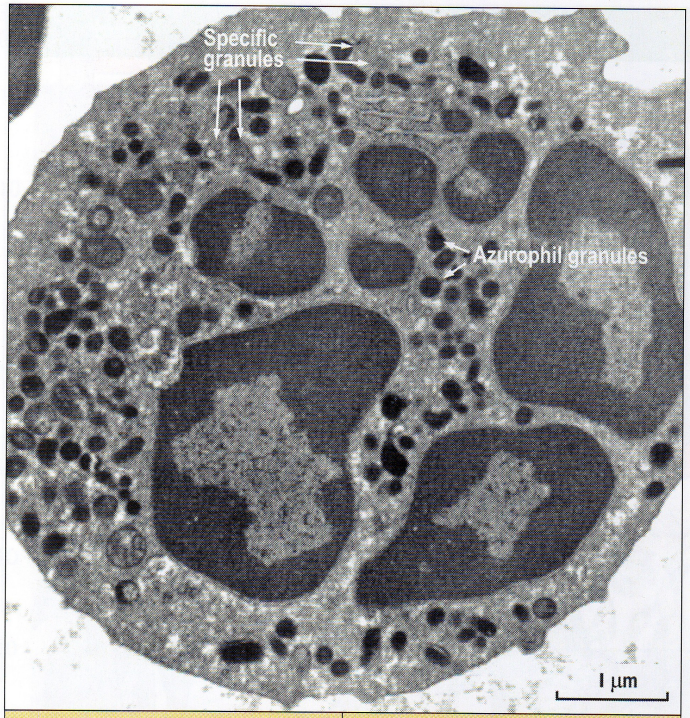
Bakterizide Agentien von Phagocyten

Class of mechanism	Specific products
Acidification	pH=~3.5–4.0, bacteriostatic or bactericidal
Toxic oxygen-derived products	Superoxide O_2^-, hydrogen peroxide H_2O_2, singlet oxygen $^1O_2^{\bullet}$, hydroxyl radical $OH^{\bullet}$, hypohalite OCl^-
Toxic nitrogen oxides	Nitric oxide NO
Antimicrobial peptides	Defensins and cationic proteins
Enzymes	Lysozyme—dissolves cell walls of some Gram-positive bacteria. Acid hydrolases—further digest bacteria
Competitors	Lactoferrin (binds Fe) and vitamin B_{12}-binding protein

Figure 2-6 Immunobiology, 6/e. (© Garland Science 2005)

Neutrophile Granulocyten als Effektoren: Unterschiedliche Granula mit spezifischen Funktionen

Primäre Granula:
Sekretion,
extrazelluläres killen
Nicht-oxidative Mechanismen



AZUROPHIL GRANULES	SPECIFIC GRANULES
0.5 μm 1500/cell	0.2 μm 3000/cell
Lysozyme Myeloperoxidase Elastase Cathepsin G H^+ hydrolases Defensins BPI	Lysozyme Cytochrome b_{558} OH^- phosphatase Lactoferrin Vitamin B_{12} binding protein

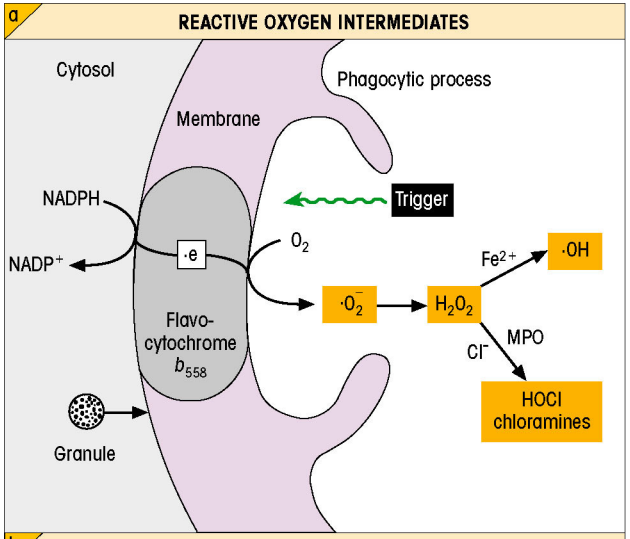
Figure 1.3. Ultrastructure of neutrophil. The multilobed nucleus and two main types of cytoplasmic granules are well displayed. (Courtesy of Dr D. McLaren.)

Sekundäre Granula:
Phagolysosom,
intrazelluläres killen
Auch oxidative Mechanismen:
Produktion von
Reactive oxidative species
während des
Oxidative burst

Vielfältige Tötungsmechanismen

Abtöten phagocytierter extrazellulärer Erreger

Abtöten von Erregern im Cytosol



c OXYGEN-INDEPENDENT MECHANISMS

Cathepsin G Low mol. wt defensins High mol. wt cationic proteins Bactericidal permeability increasing protein (BPI)	Damage to microbial membranes
Lysozyme	Splits mucopeptide in bacterial cell wall
Lactoferrin	Complex with iron
Proteolytic enzymes Variety of other hydrolytic enzymes	Digestion of killed organisms

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NADPH Oxidase-Reaktion (Cytb558-verm.):
$NADPH + 2O_2 \rightarrow NADP^+ + H^+ + 2O_2^-$ (Superoxid Anion)

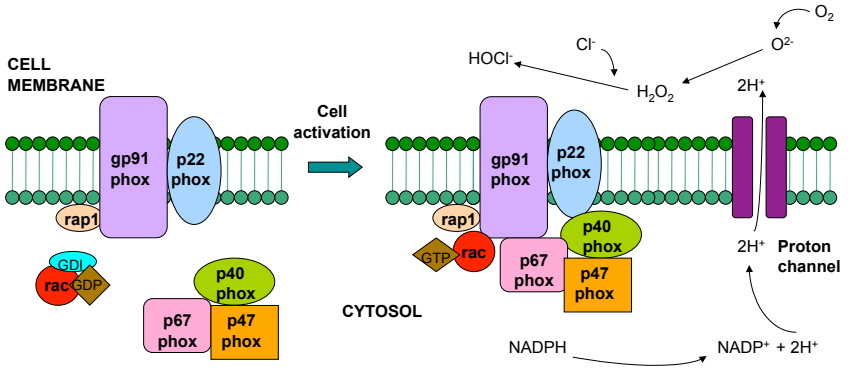
Superoxid-Dismutase Reaktion:
$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$

Myeloperoxidase Reaktion (sezerniert):
$H_2O_2 + Cl^- \rightarrow H_2O + ClO^-$ (Hypochlorit)

Chronische Granulomatose: Beeinträchtigte Phagocytenfunktion

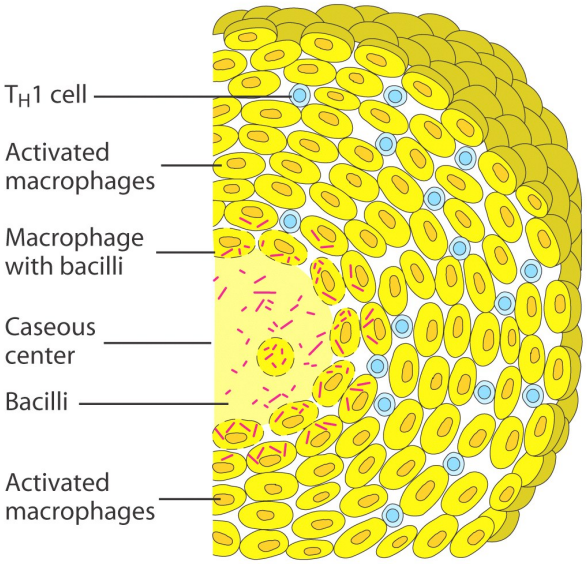
Genetische Defekte der NADPH Oxidase
Am häufigsten Mutationen des gp91^{phox}
(X-gekoppelt)

➡ Hohe Infektionsanfälligkeit,
Opportunistische Erreger
(*Aspergillus, Klebsiella, Pseudomonas* etc.)



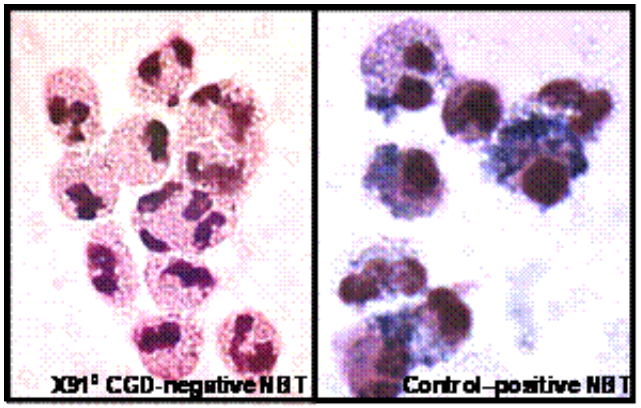
Assari *Medical Immunology 2006* ***5:4***

Persistierende Infektionen führen zur Bildung von
Granulomen in verschiedensten Organen (Pneumonien!)



Goldsby, Immunology, 5. Aufl.

Nachweis:



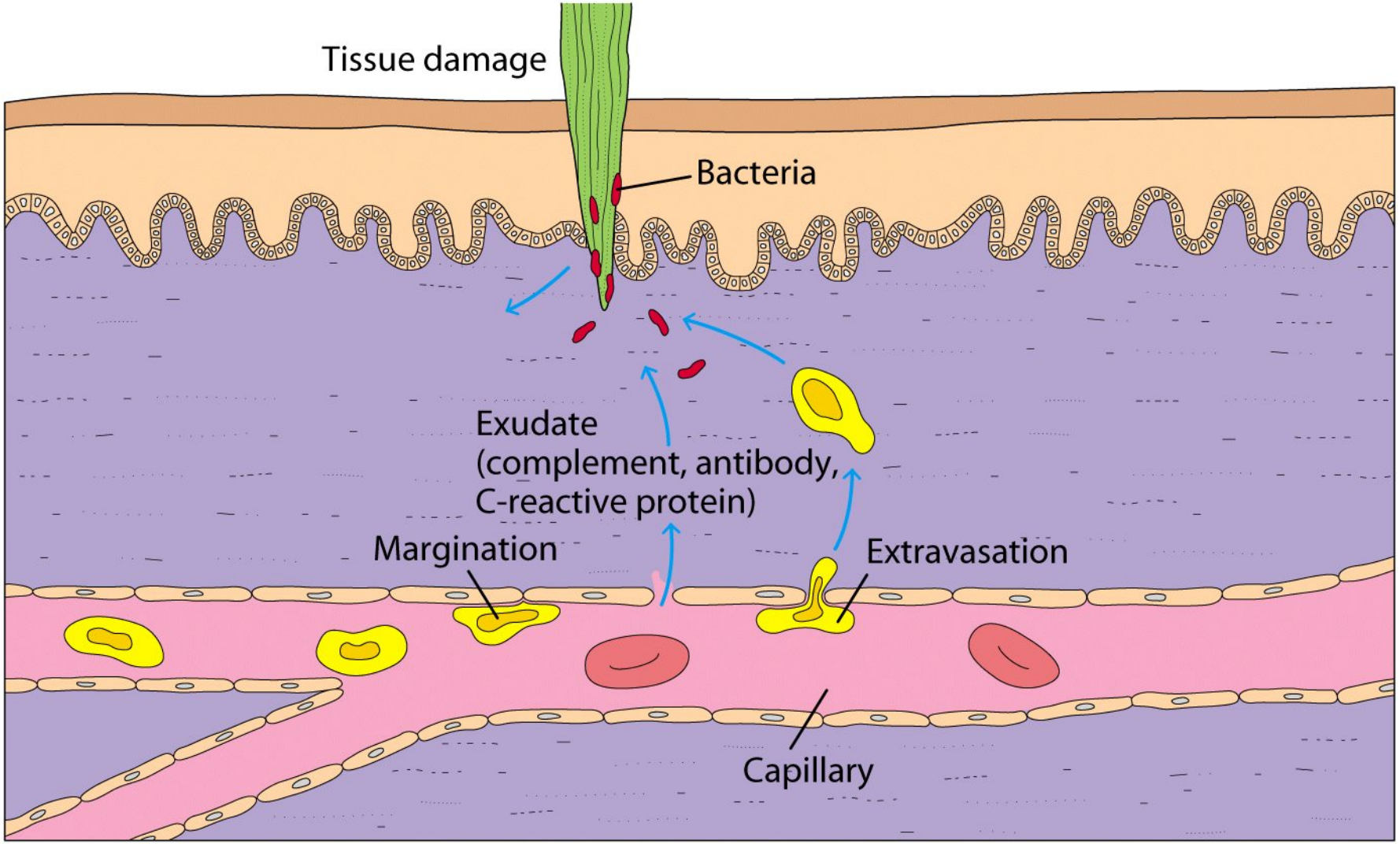
NBT reduction test

CGD Diagnosis Laboratory, Grenoble

Entzündungsreaktionen und die Entstehung adaptiver Immunantworten

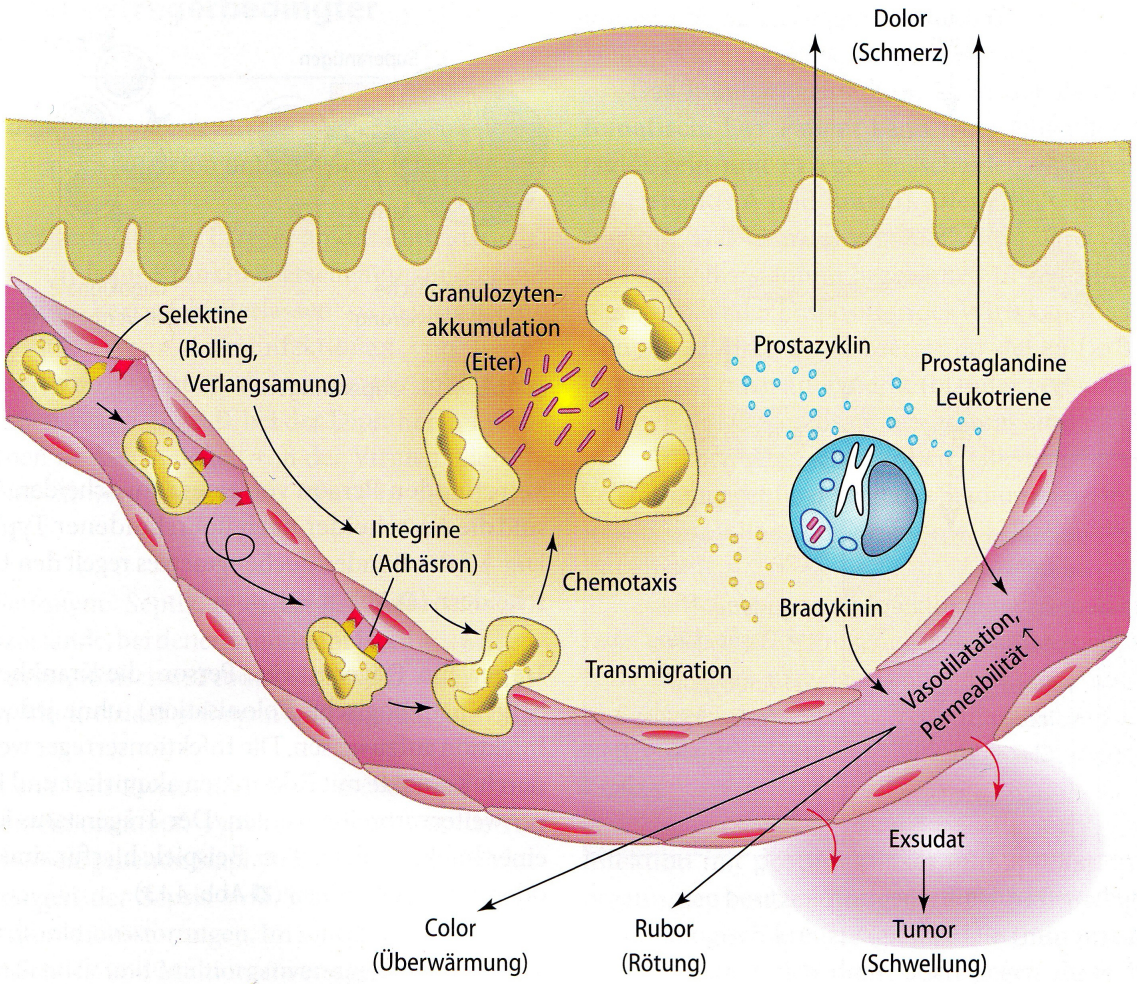
- Die akute Entzündungsreaktion
- Entzündungsfördernde (proinflammatorische) „Mastercytokine“: IL-1, IL-6, TNF
- Die Akutphase-Reaktion
- Entzündung außer Kontrolle: Septischer Schock
- Dendritische Zellen als Schnittstelle zur adaptiven Immunität

Die akute Entzündungsreaktion



Goldsby, Immunology, 5. Aufl.

Die akute Entzündungsreaktion



Hahn et al., Medizinische Mikrobiologie und Infektiologie, 6. Aufl.

Neutrophile Granulocyten locken Monocyten an: Mobile Einsatzgruppe und Totengräber des Immunsystems

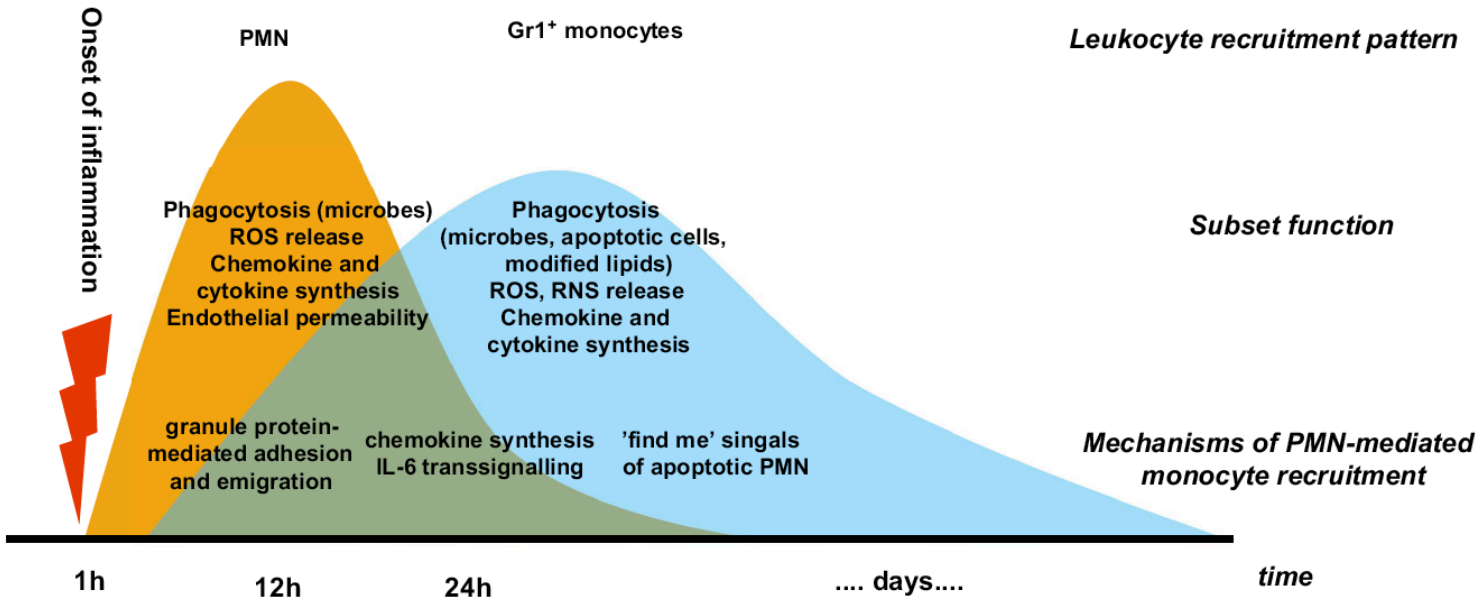


Figure 5. Integrated view of the PMN-monocyte axis in inflammation. PMNs are rapidly recruited to the site of inflammation. Granule proteins allow for almost instant recruitment of inflammatory monocytes. Mechanisms requiring de novo synthesis of adhesion molecules and chemokines come into effect at later time points. Finally, signals generated by apoptotic PMNs attract inflammatory monocytes. Thus, the axis of PMNs and Gr1$^+$ monocytes provides an acceleration of proinflammatory events.

Soehnlein et al. (2009) *Blood* 114:4613

Exkurs I: Makrophagen als Totengräber

Apoptose: Beseitigung sterbender Zellen ohne Aktivierung des Immunsystems

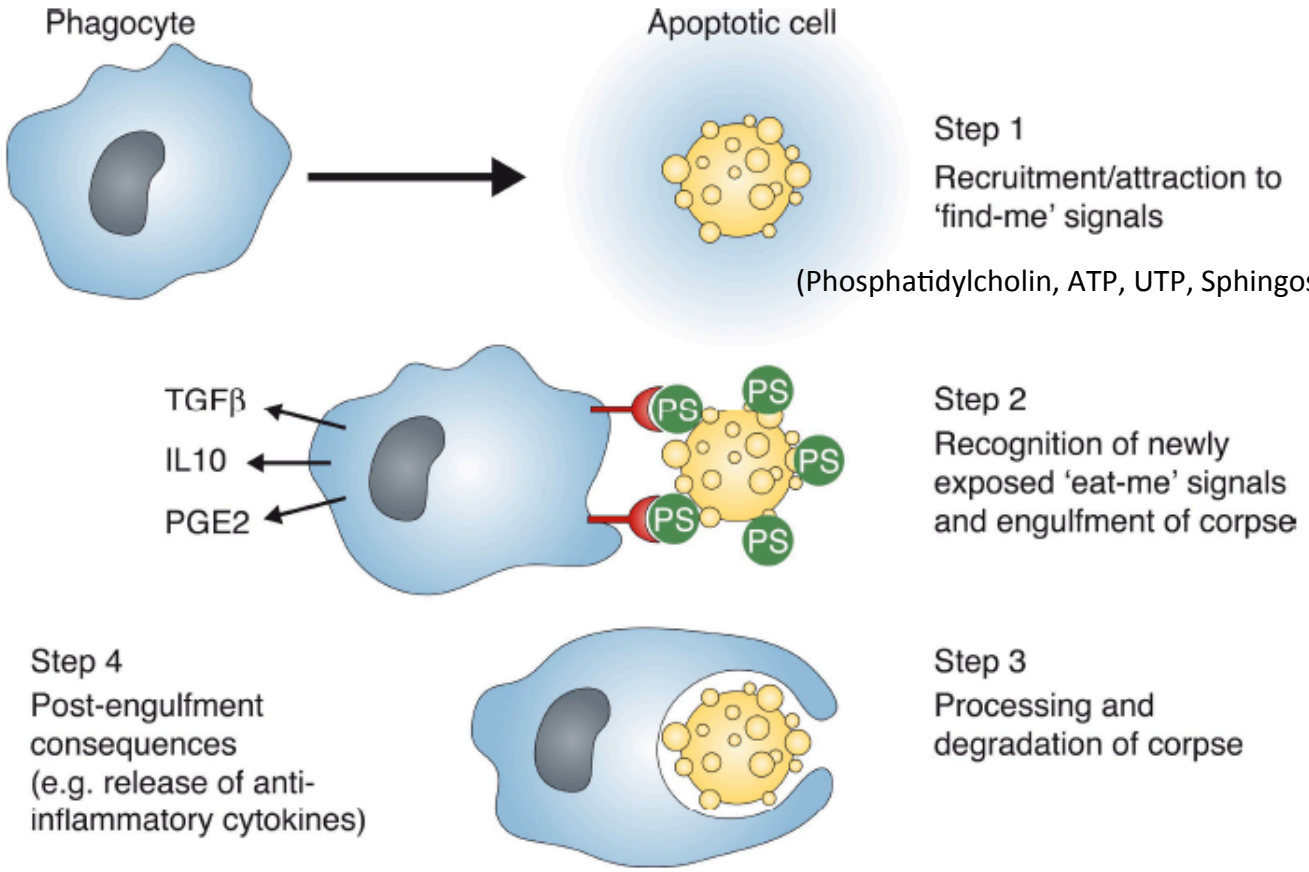
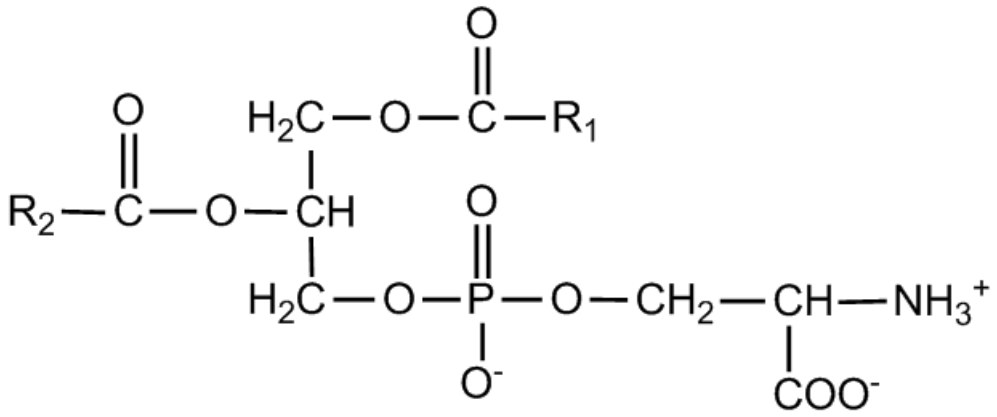
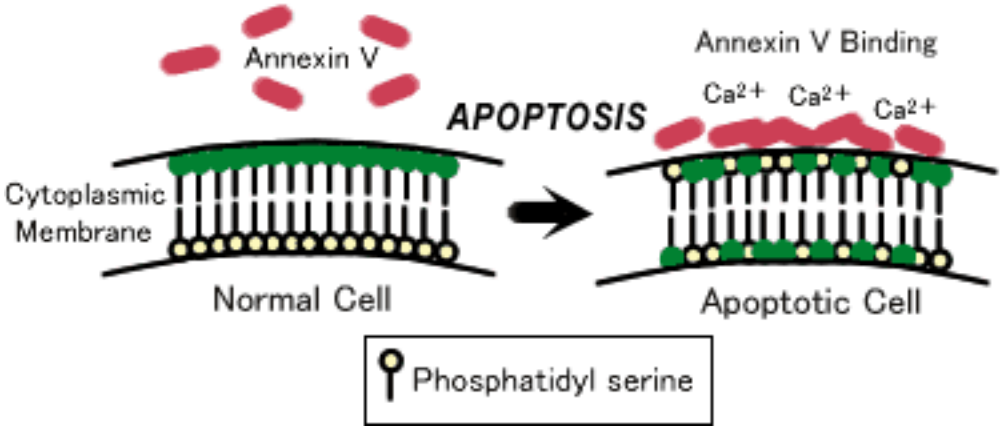


Figure 1. Different steps involved in efficient apoptotic cell clearance. The find-me signals (such as low levels of nucleotides ATP and UTP, fractalkine, lysophosphatidylcholine, or sphingosine 1-phosphate) released by apoptotic cells help attract motile phagocytes to the proximity of the cell undergoing apoptosis. The phagocytes then use engulfment receptors on their surface to engage eat-me signals on apoptotic cells. For clarity, only the PtdSer on the apoptotic cells engaged by cognate receptors is depicted. Engagement of the engulfment receptors (linked to PtdSer recognition) has been shown to stimulate release of antiinflammatory cytokines such as TGF-β, IL-10, and prostaglandin E2 (PGE2). The intracellular signaling induced within the phagocyte by the ligand–receptor interactions leads to cytoskeletal rearrangements and internalization of the dying cell. The phagocyte processes the engulfed corpse through a series of steps, and proper digestion seems to be important for continued uptake of other dying cells by phagocytes.

Ravichandran *2010 J Exp Med* 207:1807

Exposition des Membranlipids Phoshatidylserin auf apoptotischen Zellen: Eat me Signal





Exkurs II: Sterile Entzündungen

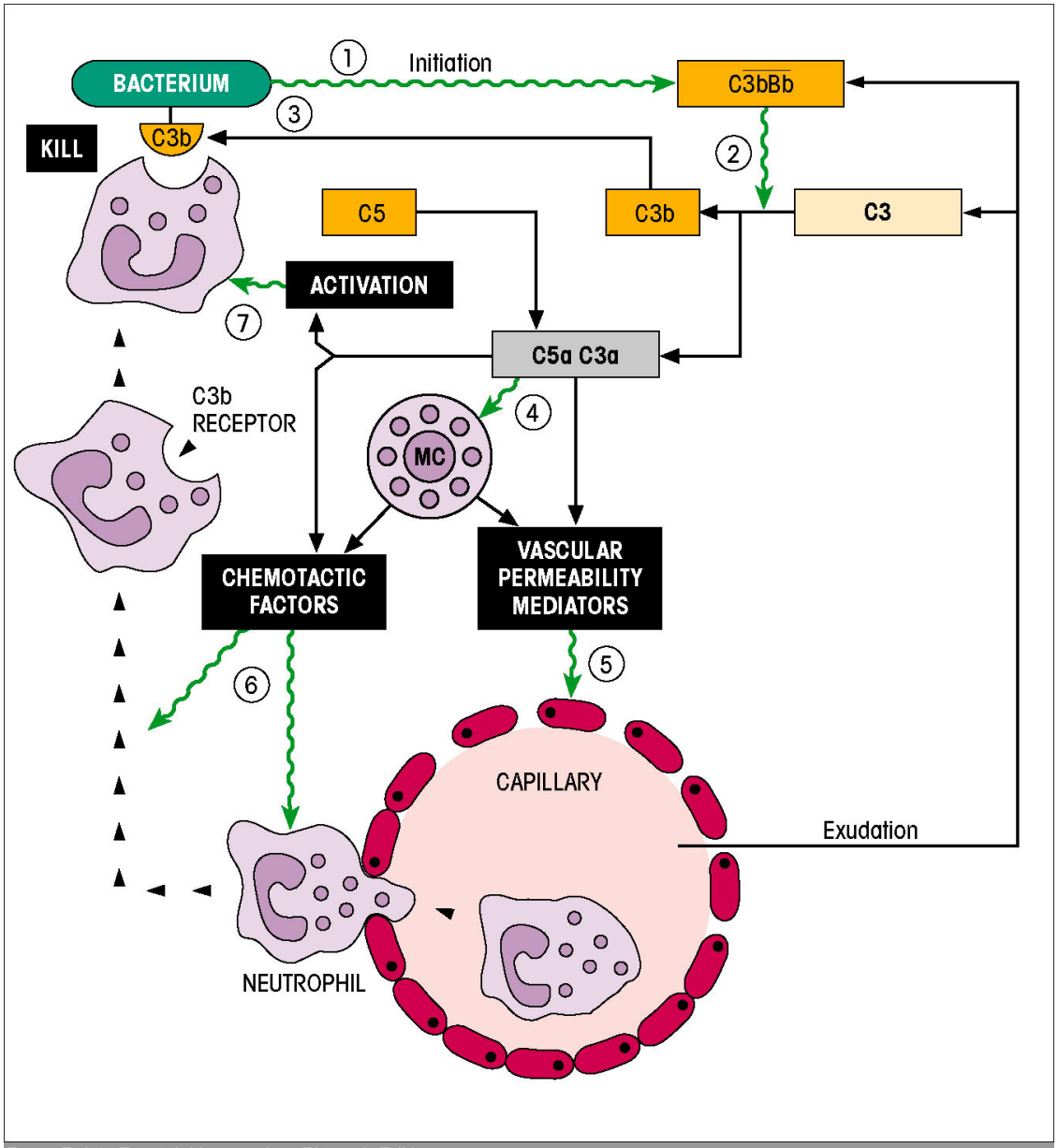
Aktivierung von Pattern Recognition Receptors durch nicht-mikrobielle Liganden:

Danger associated molecular patterns (DAMPs) oder Alarmine

Typisch als Folge von Nekrosen nach Ischämien und Traumata

Freisetzung zelleigener Substanzen, die normalerweise (Apoptose!)
für das Immunsystem nicht erreichbar sind
(z. B. ATP, DNA, RNA, HMGB1, S100 Proteine etc.)

Die Mastzelle als Initiator der akuten Entzündungsreaktion



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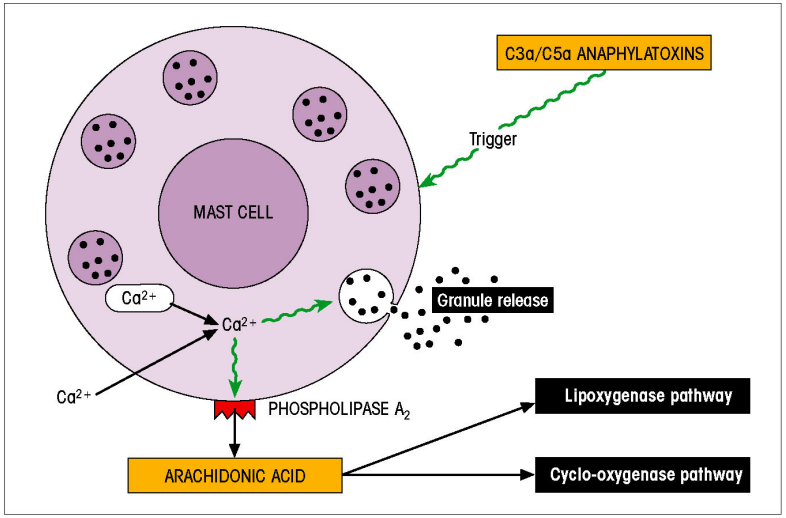
Die Mastzelle setzt entzündungsfördernde Mediatoren (Histamin, TNF) schnell frei



	PRE-FORMED	EFFECT
Granule release ►	HISTAMINE	Vasodilatation, incr. capillary permeability chemokinesis, bronchoconstriction
	PROTEOGLYCAN	Binds granule proteases
	NEUTRAL PROTEASES β-GLUCOSAMINIDASE	Activates C3 Splits off glucosamine
	ECF NCF	Eosinophil chemotaxis Neutrophil chemotaxis
	PLATELET ACTIVATING FACTOR	Mediator release
	INTERLEUKINS 3,4, 5 & 6 GM-CSF, TNF	Multiple, including macrophage activation, trigger acute phase proteins, etc. (cf. Chapter 9)

	NEWLY SYNTHESIZED	EFFECT
Lipoxygenase pathway ►	LEUKOTRIENES C_4, D_4 (SRS-A), B_4	Vasoactive, bronchoconstriction, chemotaxis
Cyclo-oxygenase pathway ►	PROSTAGLANDINS THROMBOXANES	Affect bronchial muscle, platelet aggregation and vasodilatation

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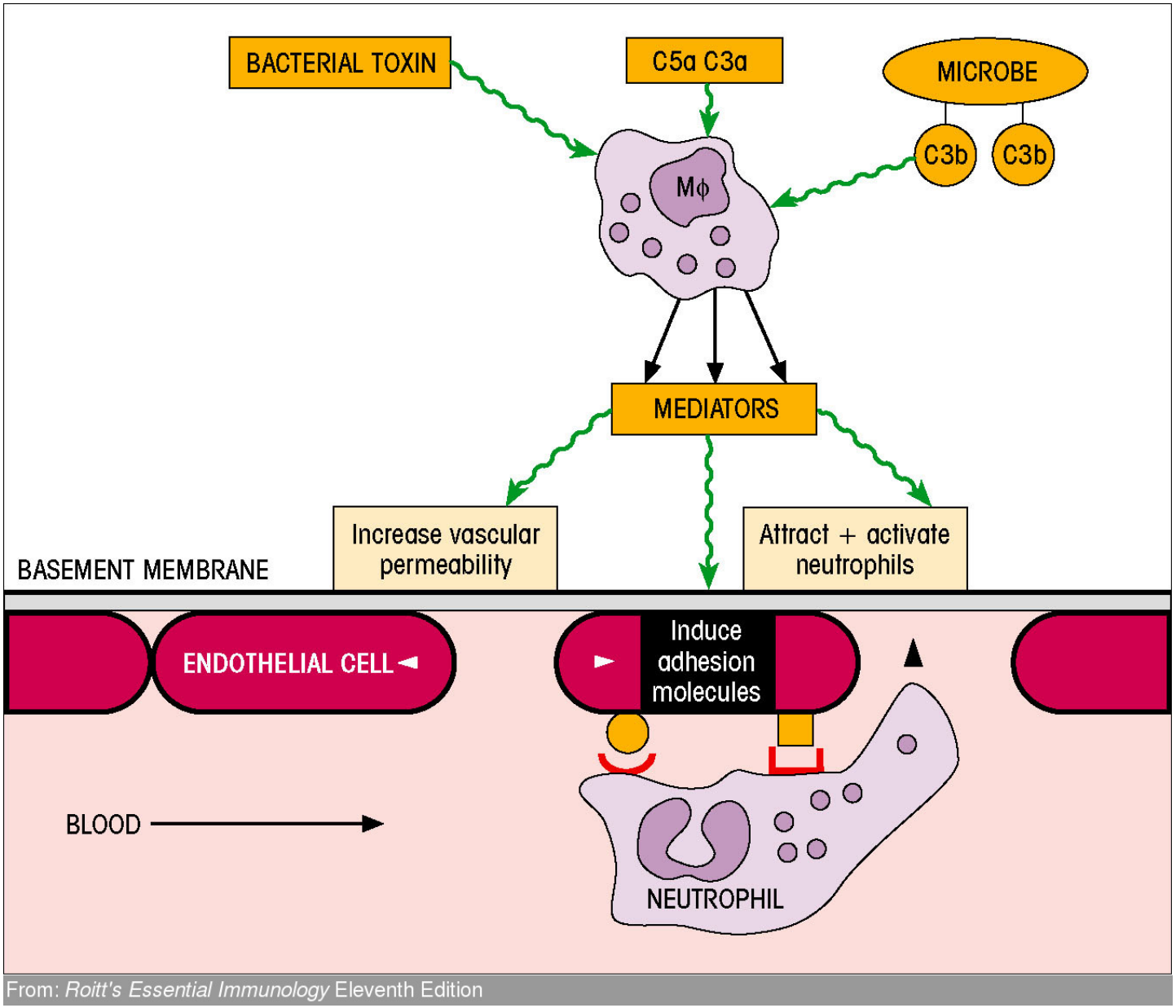
Der Makrophage kann es auch. Nur nicht so schnell !



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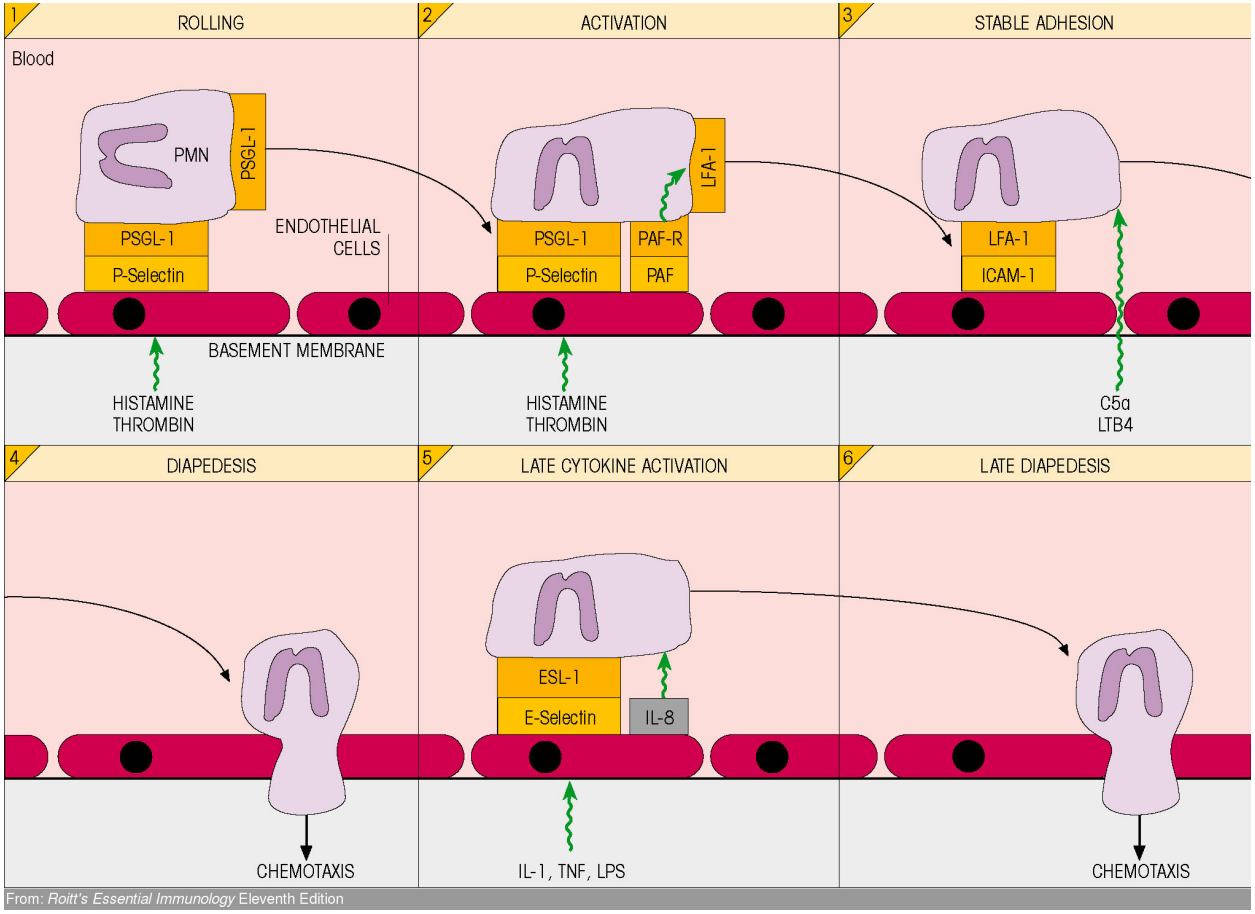
Aktivierung des Gefäßendothels



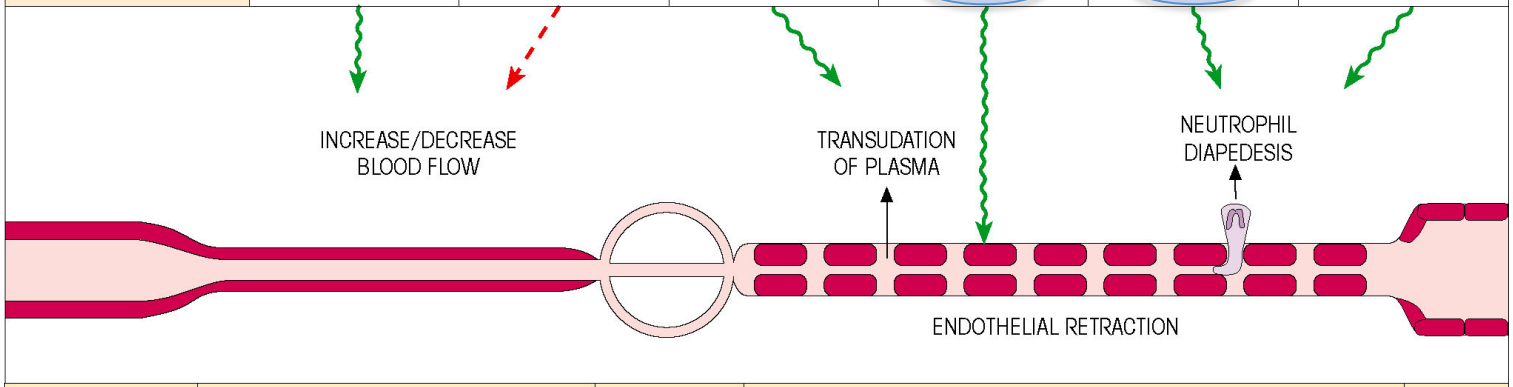
Stufe 1: „Rolling“ Reversible Bindung (Bremsfallschirm)
Schnelle Expression von P-Selectin (intrazellulär gespeichert in Weibel-Palate Körpern, dient Abbremsung der Neutros durch Bindung an fucosylierte Kohlenhydratketten). Induziert durch LTB4, C5a, Histamin, TNF, LPS.
Nach 1-2 hrs kommt E-Selektin hoch, de novo Synthese induziert durch Cytokine u. LPS

Stufe 2:
Integrine auf Neutrophilen (LFA-1, CR3 (CD11b:CD18 oder auch Mac-1) binden an ICAM-1 und ICAM-2 auf Endothelzellen.
Integrinbindung wird durch Chemokine gesteigert („inside out signaling“) und führt zu stabiler Bindung

Stufe 3:
Diapedese durch Basallmembran mittels Enzyme. Durch Chemokine verstärkt.

Stufe 4: Wanderung im Gewebe unter Einfluß von Chemokinen.

MEDIATOR ACTION						
	DILATATION	CONSTRICTION	INCREASE PERMEABILITY	UPREGULATE ADHESION MOL.		NEUTROPHIL CHEMOTAXIS
				ENDOTHELIUM	NEUTROPHIL	
HISTAMINE	+		+	++		
BRADYKININ	+		++			
PGE_2/I_2	+++		Potentiate other mediators			
VIP	+++					
NITRIC OXIDE	+++		+++			
LEUKOTRIENE-D4		+				
LEUKOTRIENE-C4		++	+			
C5a			++	+	++	+++
LEUKOTRIENE-B4			++		++	+++
f.Met.Leu.Phe			++		+	+
PLATELET ACTIVATING FACTOR	+		++		++	
IL-8					+++	+++
NAP-2 (CXCL7)					++	++
IL-1				++	++	
TNF				++	++	



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Entzündungsförderne (proinflammatorische) „Mastercytokine“

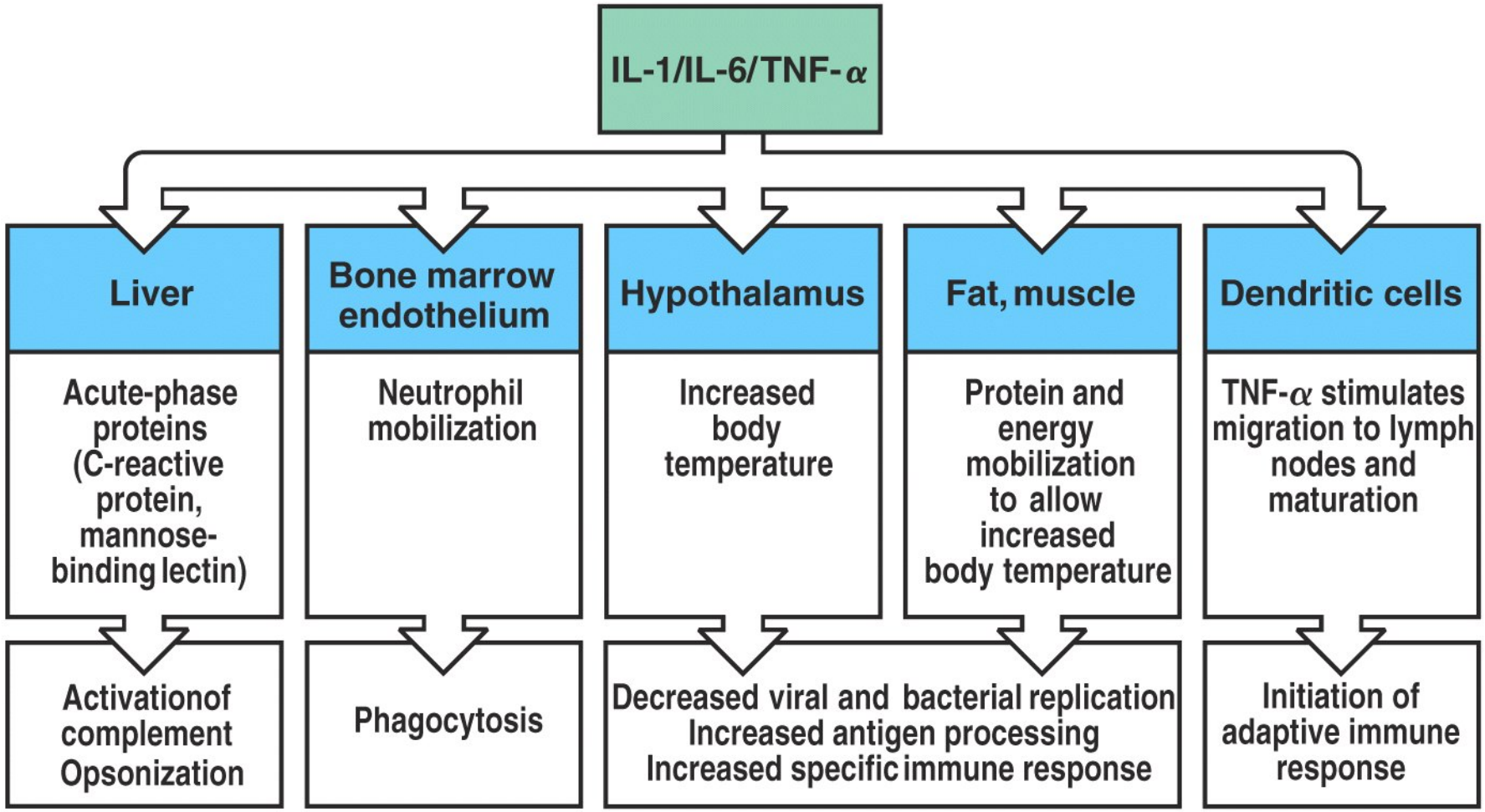
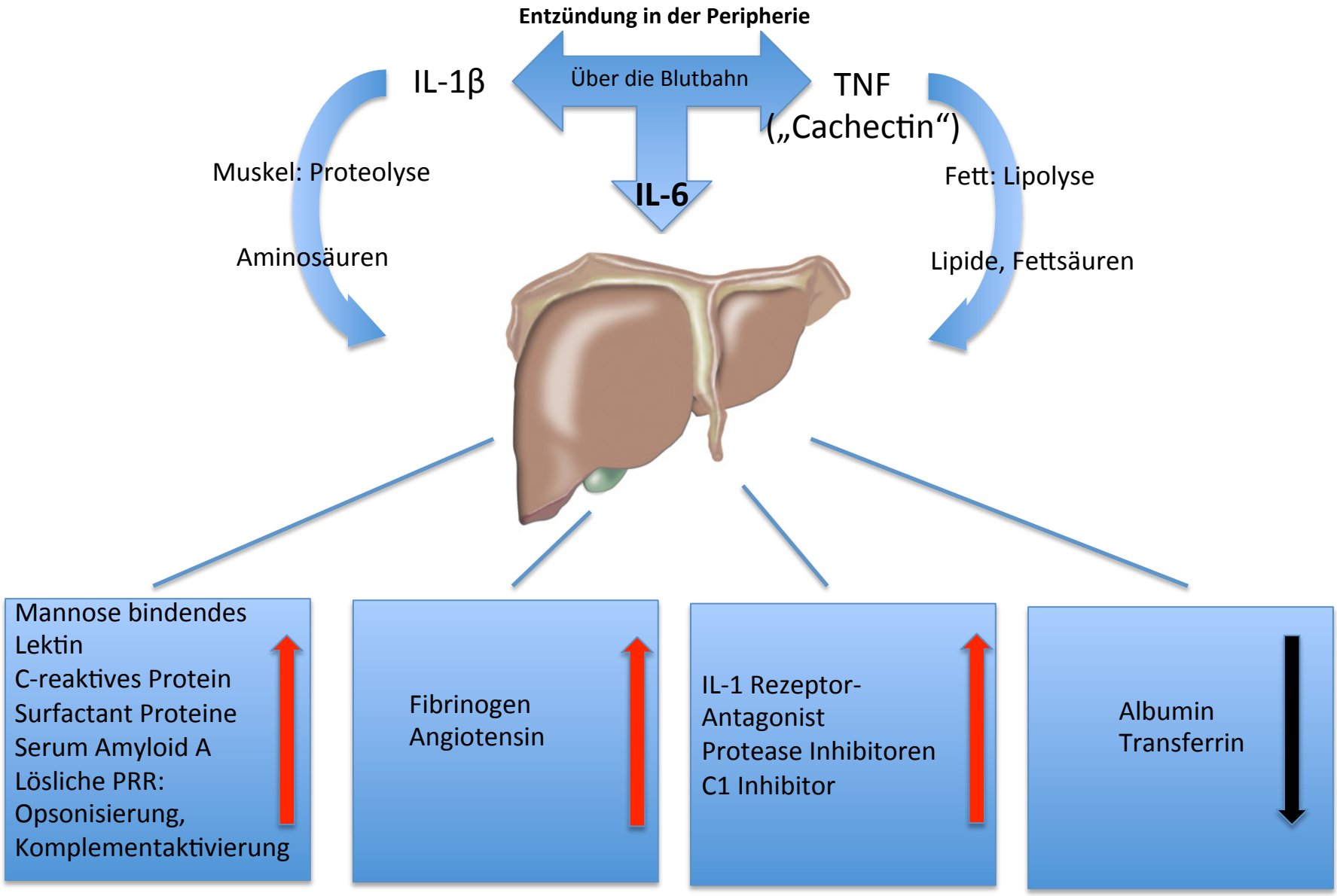


Figure 2-46 Immunobiology, 6/e. (© Garland Science 2005)

Die Akutphase-Reaktion



Septischer Schock: Das Immunsystem bedroht den Wirt

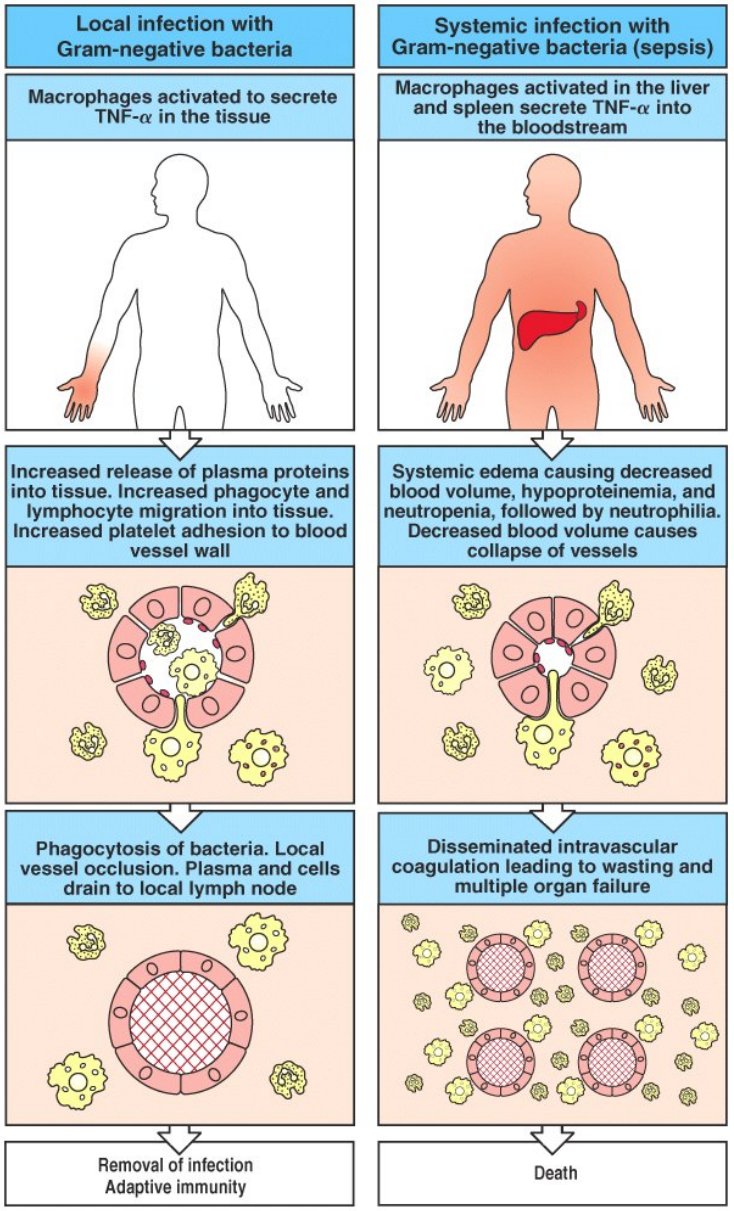
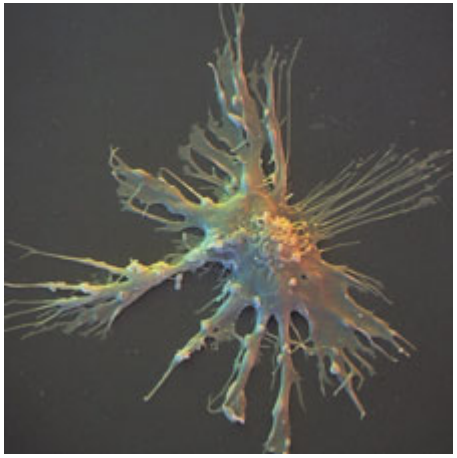


Figure 2-45 Immunobiology, 6/e. (© Garland Science 2005)

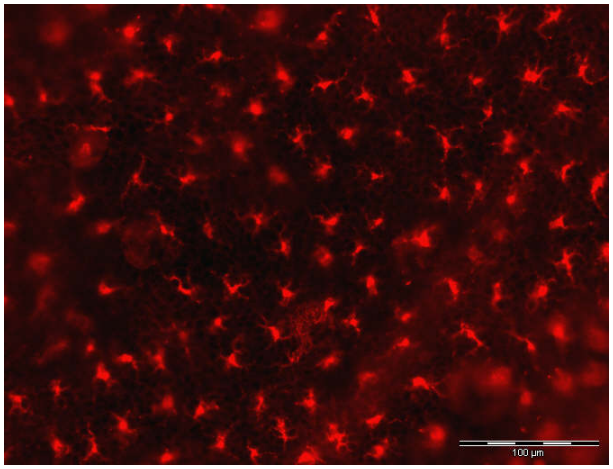
Dendritische Zellen: Wächter und Bindeglied zur adaptiven Immunität

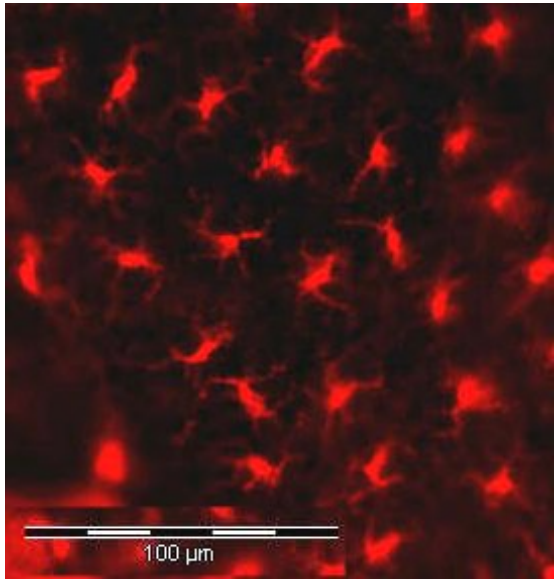
Dendritische Zellen:



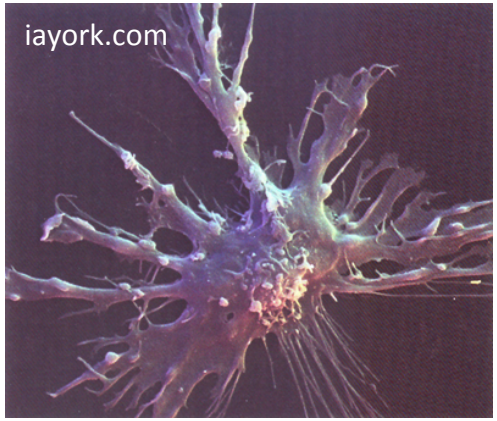
In den zentralen und peripheren lymphoiden Organen,
In der Haut (Langerhans Zellen)

Antigenpräsentation
Toleranzinduktion

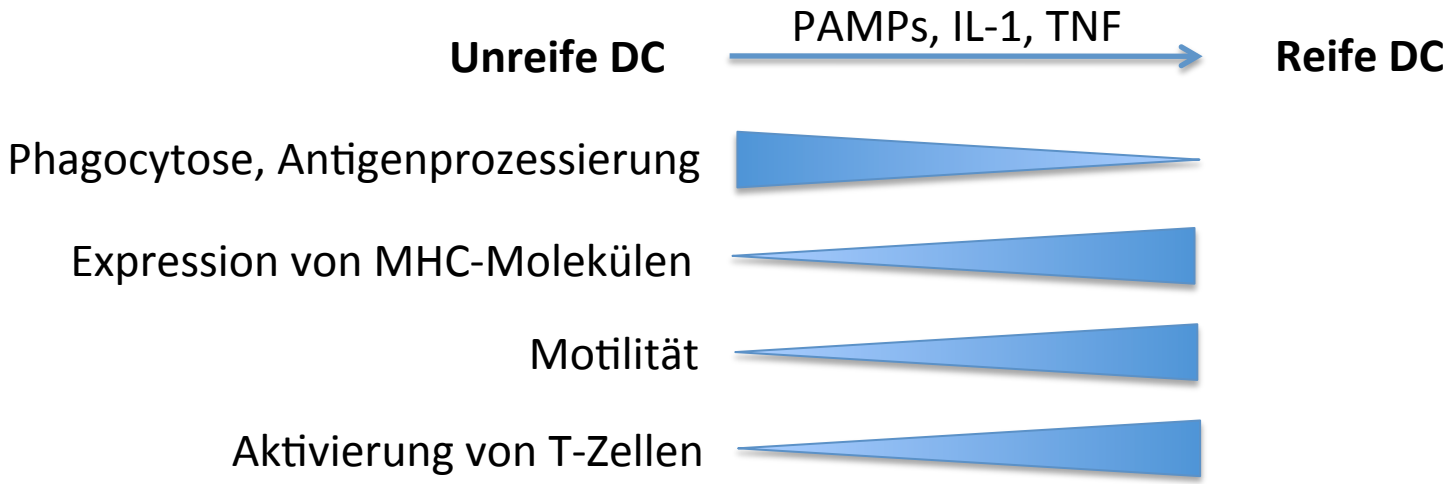




Dendritische Zellen (DC): Schnittstelle zwischen angeborener und adaptiver Immunität



- Phagocytose von „Fremd“, Abbau von Proteinen zu Peptiden
- Präsentation der Peptide zusammen mit körpereigenen Major Histocompatibility Complex (MHC) Molekülen
- Aktivierung spezifischer T-Zellen in lokalen Lymphknoten



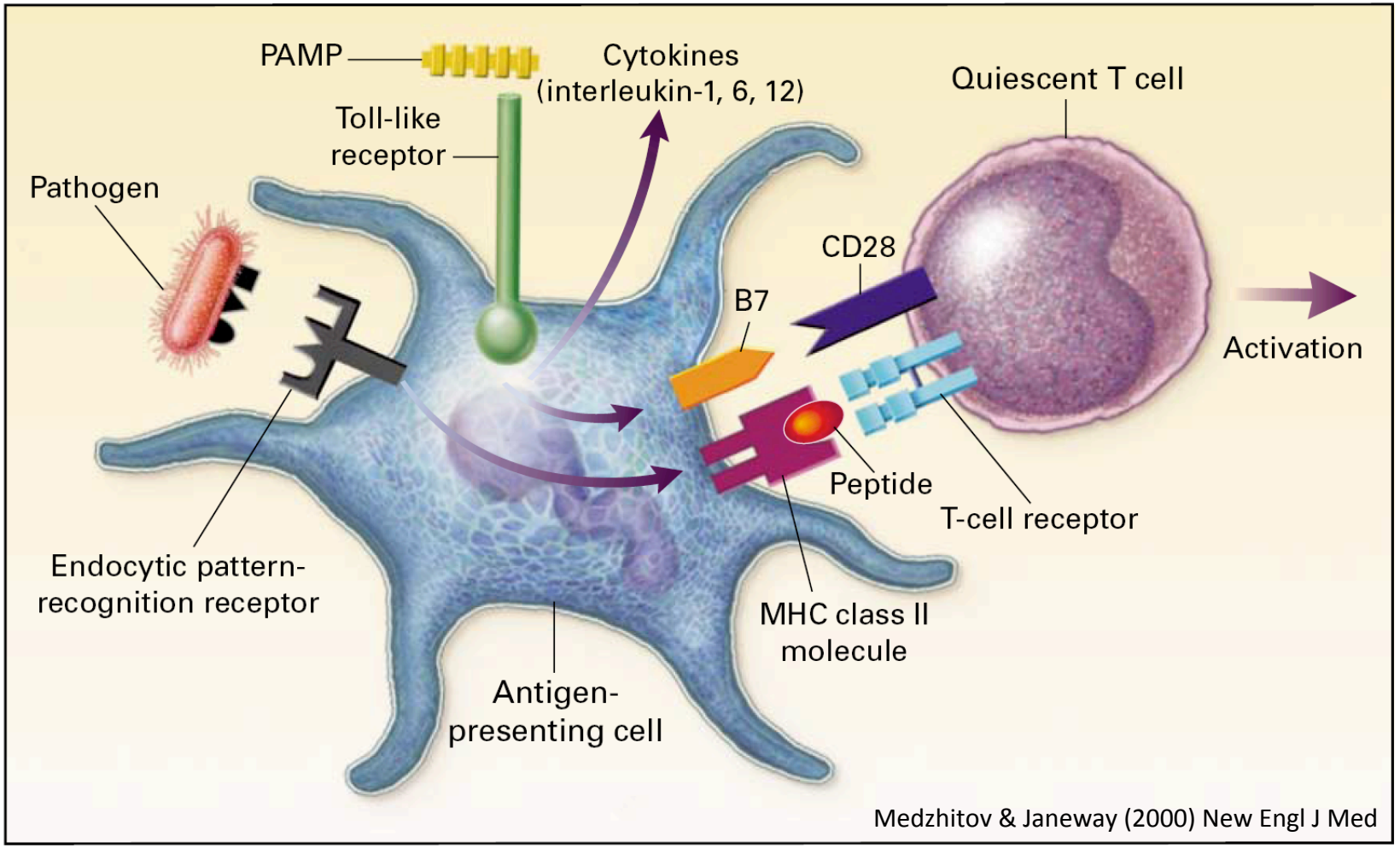


Figure 3. The Receptors Involved in the Interplay of the Innate and Adaptive Immune Systems.

Recognition of the pathogen-associated molecular pattern (PAMP) by pattern-recognition receptors, such as the toll-like receptors, generates signals that activate the adaptive immune system. Endocytic pattern-recognition receptors, such as the macrophage mannose receptor, bind to components of microbial cell walls and mediate the uptake and phagocytosis of pathogens by antigen-presenting cells (macrophages and dendritic cells). Proteins derived from the microorganisms are processed in the lysosomes to generate antigenic peptides, which form a complex with major-histocompatibility-complex (MHC) class II molecules on the surface of the macrophage. These peptides are recognized by T-cell receptors. In the case of the signaling class of pattern-recognition receptors, the recognition of pathogen-associated molecular patterns by toll-like receptors leads to the activation of signaling pathways that induce the expression of cytokines, chemokines, and costimulatory molecules. Therefore, pattern-recognition receptors have a role in the generation of both the peptide–MHC-molecule complex and the costimulation required for the activation of T cells.