

IL SANGUE

SISTEMA BIFASICO

FASE LIQUIDA (assimilabile alla matrice extrac.)

PLASMA

FASE SOLIDA (componente corpuscolare)

CELLULE NUCLEATE (g. bianchi)

CELLULE ANUCLEATE (g. rossi)

FRAMMENTI CITOPLASMATICI (piastrine)

pH 7.2-7.4, peso specifico = 1041-1062

7% peso corporeo

FUNZIONI

Respiratoria: (trasporto O_2 e CO_2)

Nutritiva: (assunzione delle sostanze nell'intestino, trasporto nel fegato per successiva elaborazione, trasporto alle cellule)

Escretrice: (trasporto cataboliti ai reni)

Termoregolazione

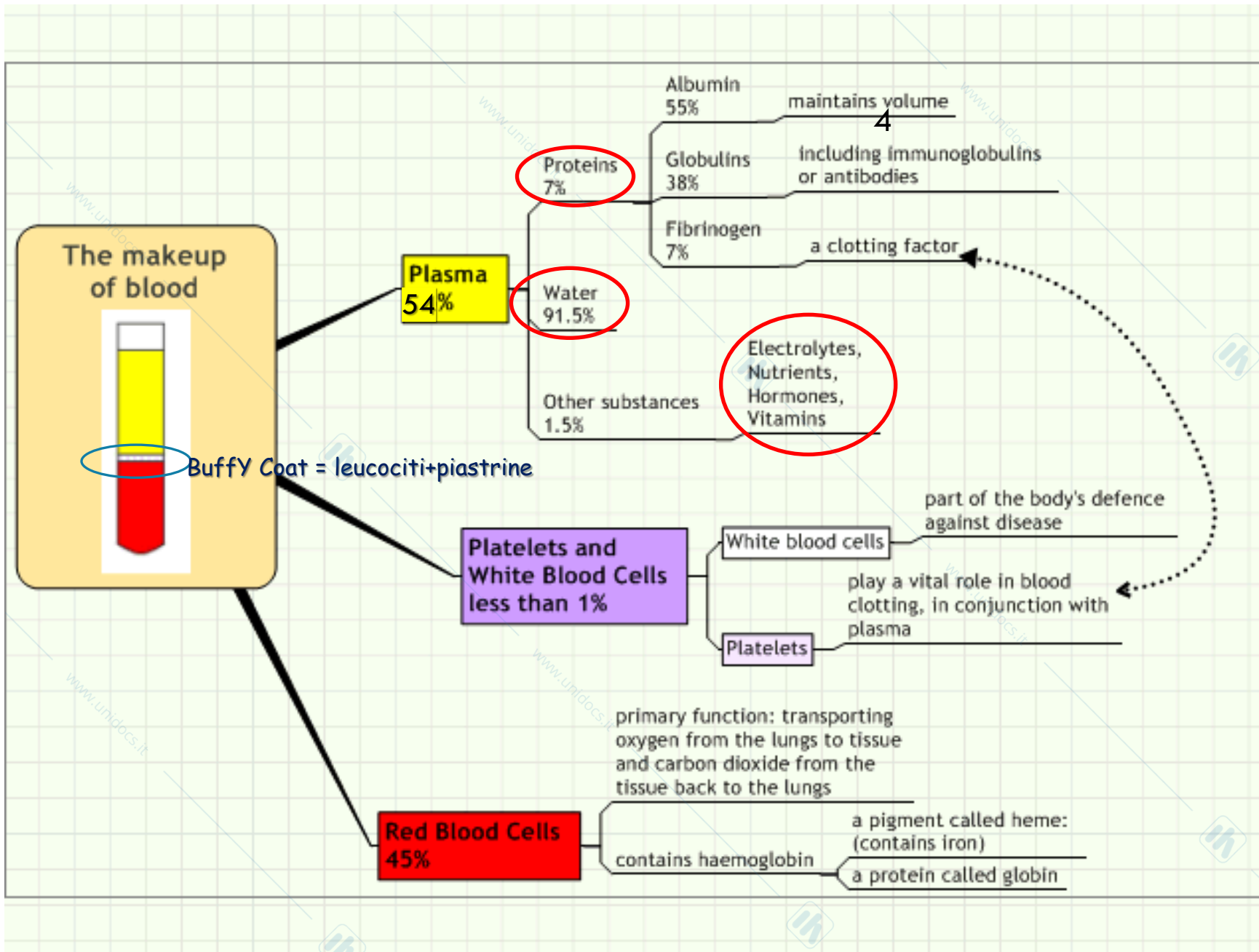
Regolazione:(trasporto di ormoni, fattori di crescita etc)

Difesa

Mantenimento della pressione oncotica

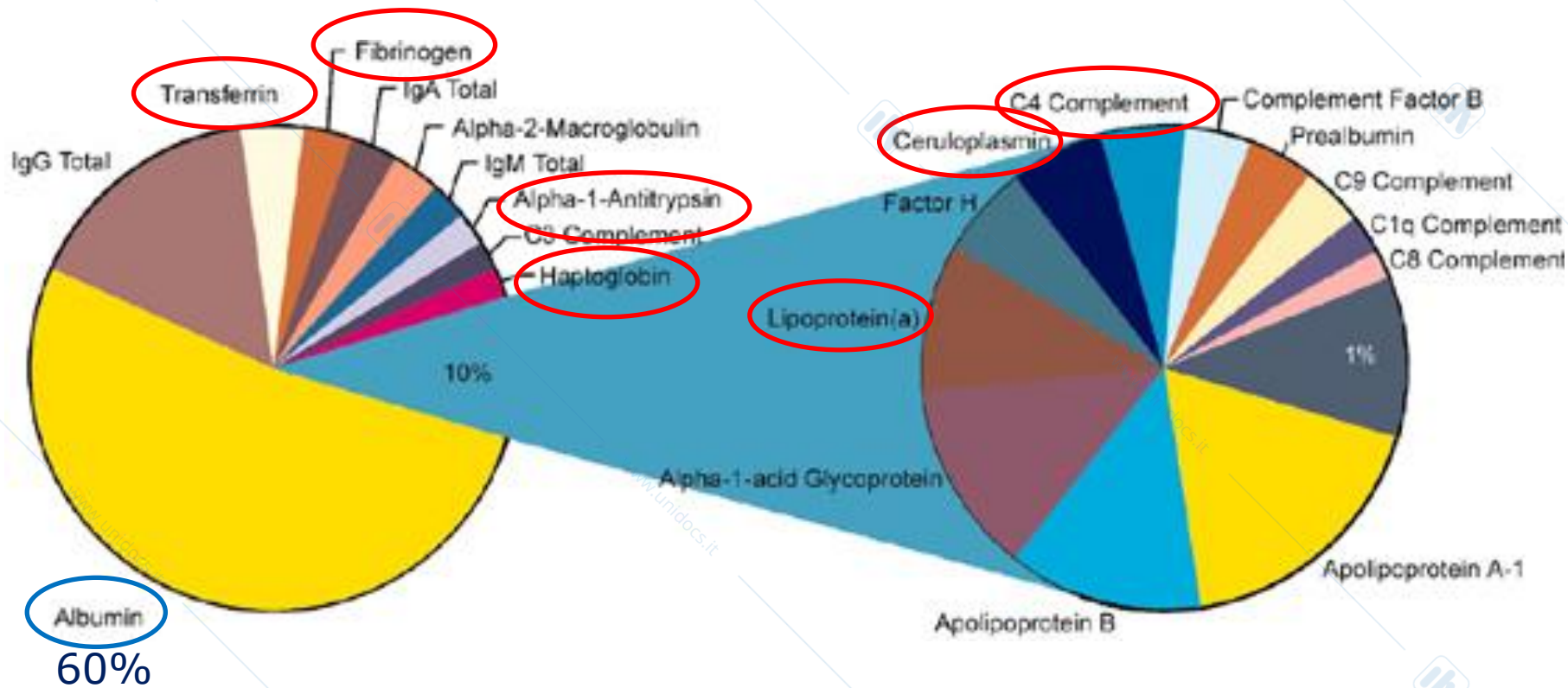
Regolazione dell'emostasi

Mantenimento dell'equilibrio acido-base

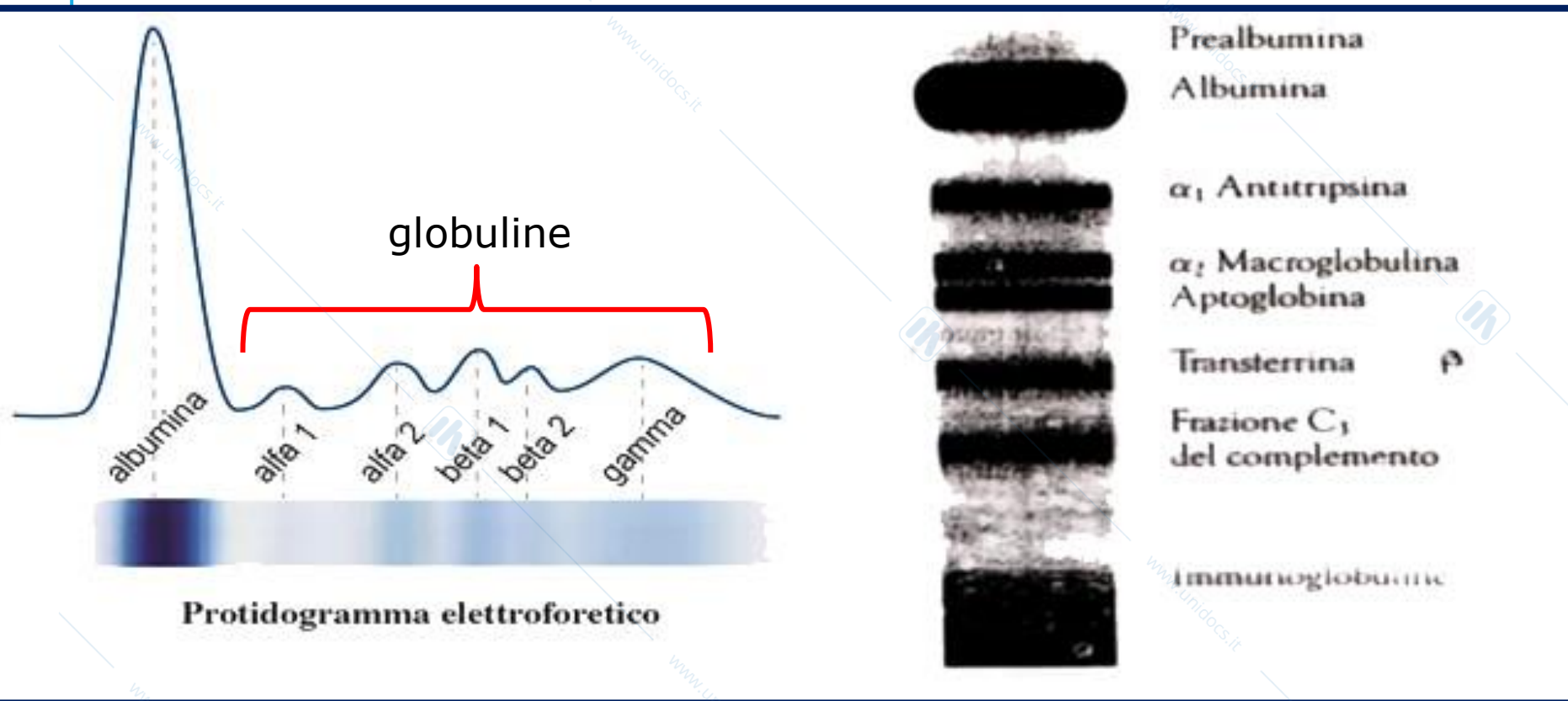


PROTEINE DEL SANGUE

Prodotte principalmente nel fegato, regolano la pressione osmotica colloidale e la viscosità del sangue. 60-70 mg/ml plasma



ELETTROFORESI



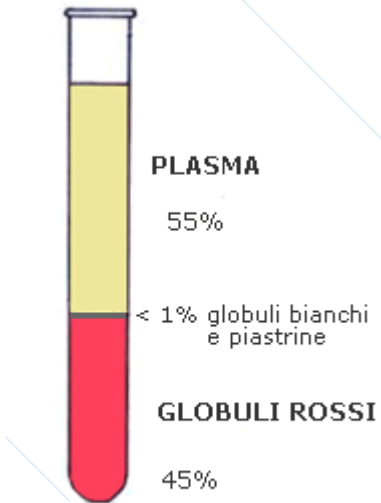
Alfa1: α_1 -antitripsina, transcortina, Fattori della coag. II, VII, X

Alfa2: α_2 -macroglobulina, aptoglobina, ceruloplasmina, Fattore IX della coagulazione

Beta 1 e 2: β_2 -macroglobulina, fibrinogeno, lipoproteine, Fattore V della coagulazione, Transferrina, frazioni C3/C4 del complemento

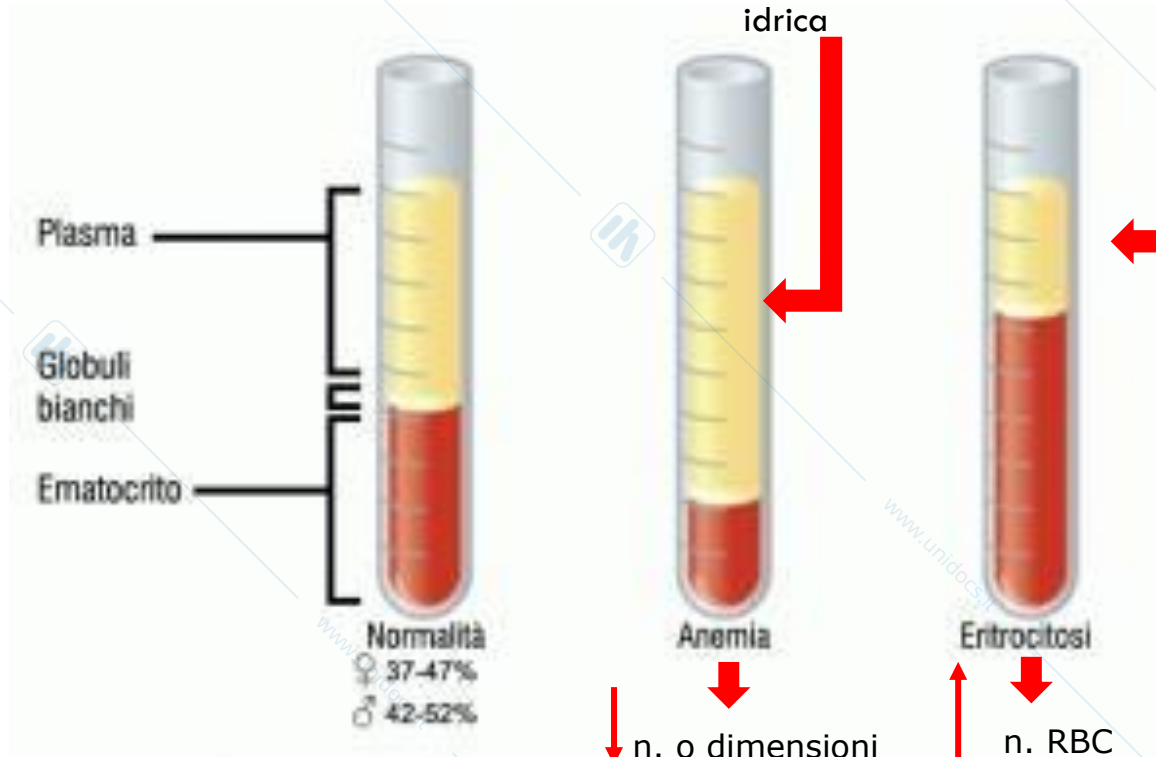
Gamma: Immunoglobulina (IgGA, M, IgG), Fattore XI della coag., frazione C8C1q del complemento, Proteina C reattiva.

EMATOCRITO



Ematocrito = 45%

45-60% neonati



EMOGRAMMA NORMALE

- Eritrociti 4-6 milioni/mmc
- Leucociti 4-10 mila/mmc
- Piastrine sino a 350000/mmc

Formula Leucocitaria:

- Linfociti 20-35%
- Monociti 3-7%
- Neutrofili 55-65%
- Eosinofili 0-3%
- Basofili 0-2%

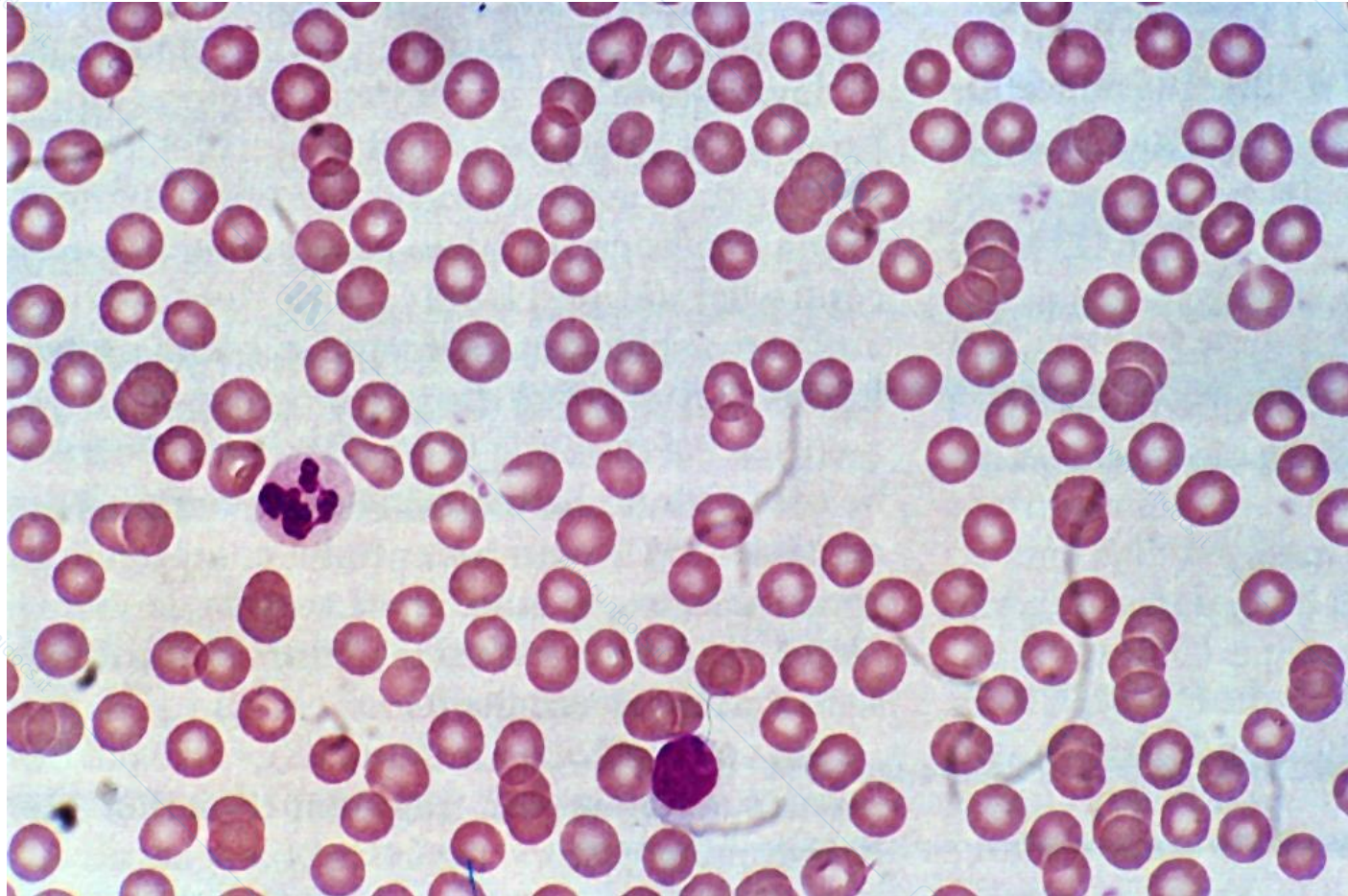
STRISCIO DI SANGUE

Miscele Romanosky (1891):

- Miscela May-Grunwald/Giemsa
- Miscela di Wright

Coloranti acidi (eosina) + coloranti basici (blu di metilene e prodotti di ossidazione del blu di metilene [azzurri]) + coloranti neutri non dissociati (eosinato di blu di metilene)

STRISCIO DI SANGUE



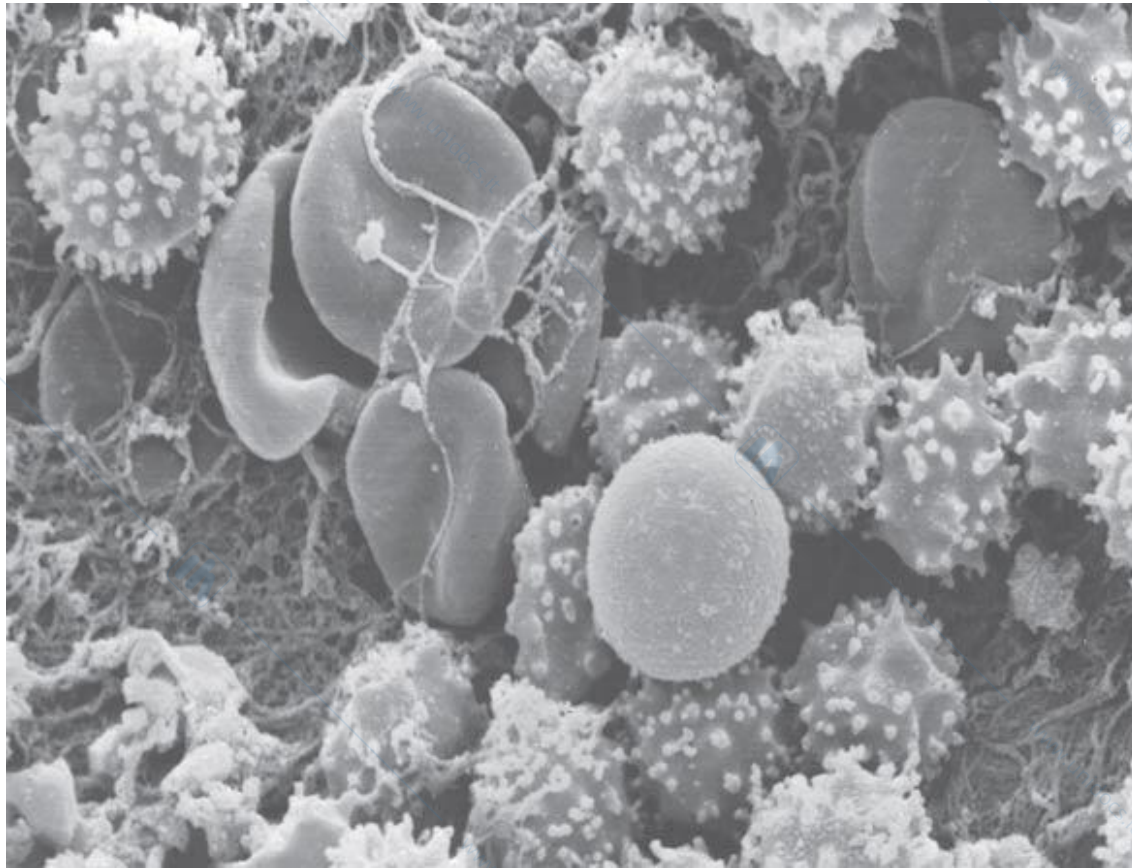
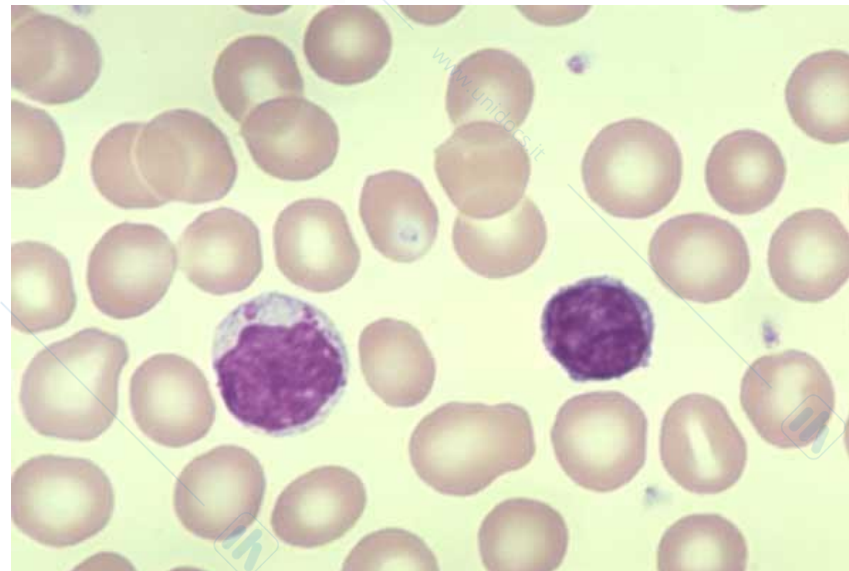
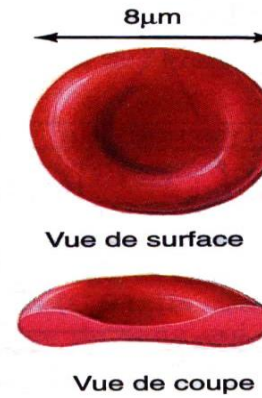


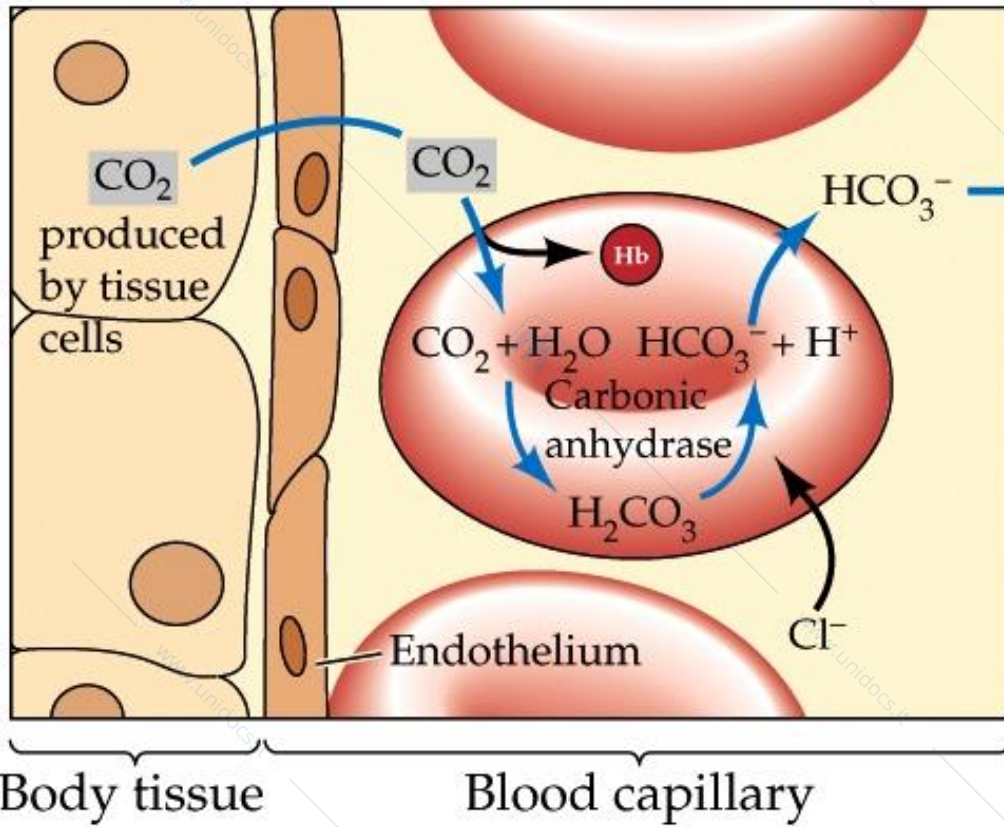
Figure 23–36 Scanning electron micrograph of mammalian blood cells caught in a blood clot. The larger, more spherical cells with a rough surface are white blood cells; the smoother, flattened cells are red blood cells. (Courtesy of Ray Moss.)

ERITROCITI (RBC)



ERITROCITI

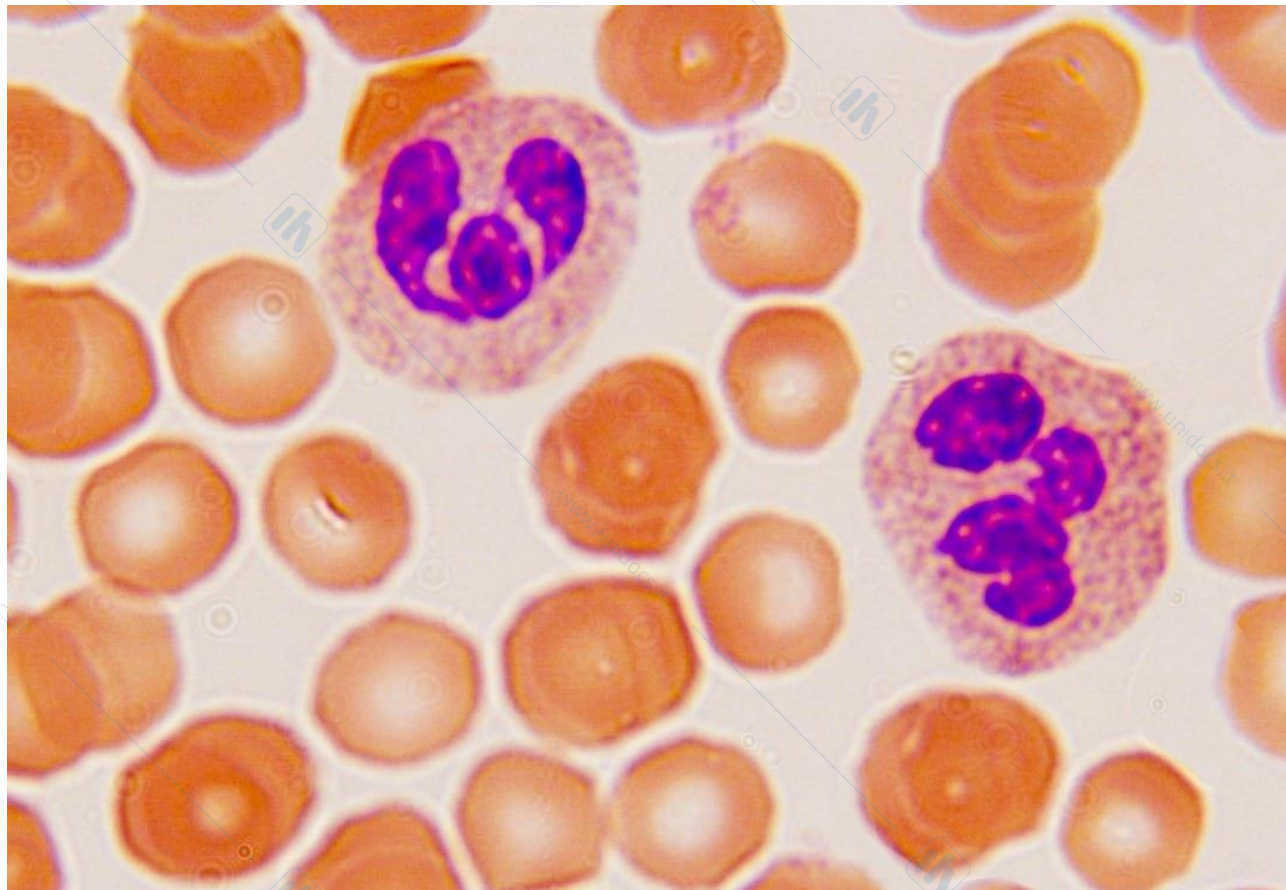
(a) In body tissue



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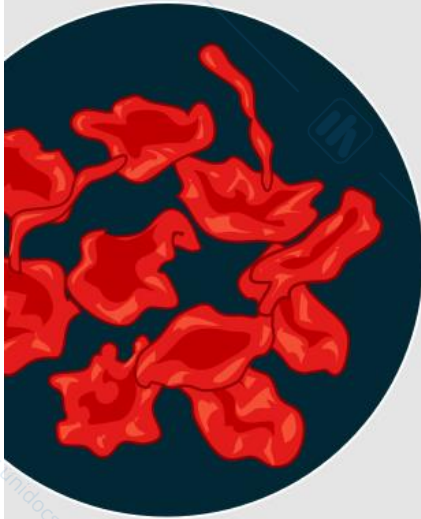
ERITROCITI

May-Grunwald-Giemsa: Acidofili per la presenza di HGB



ERITROCITI E PRESSIONE OSMOTICA

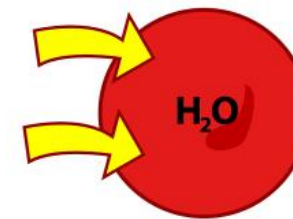
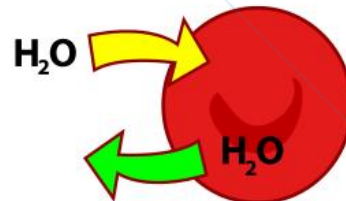
Hypertonic



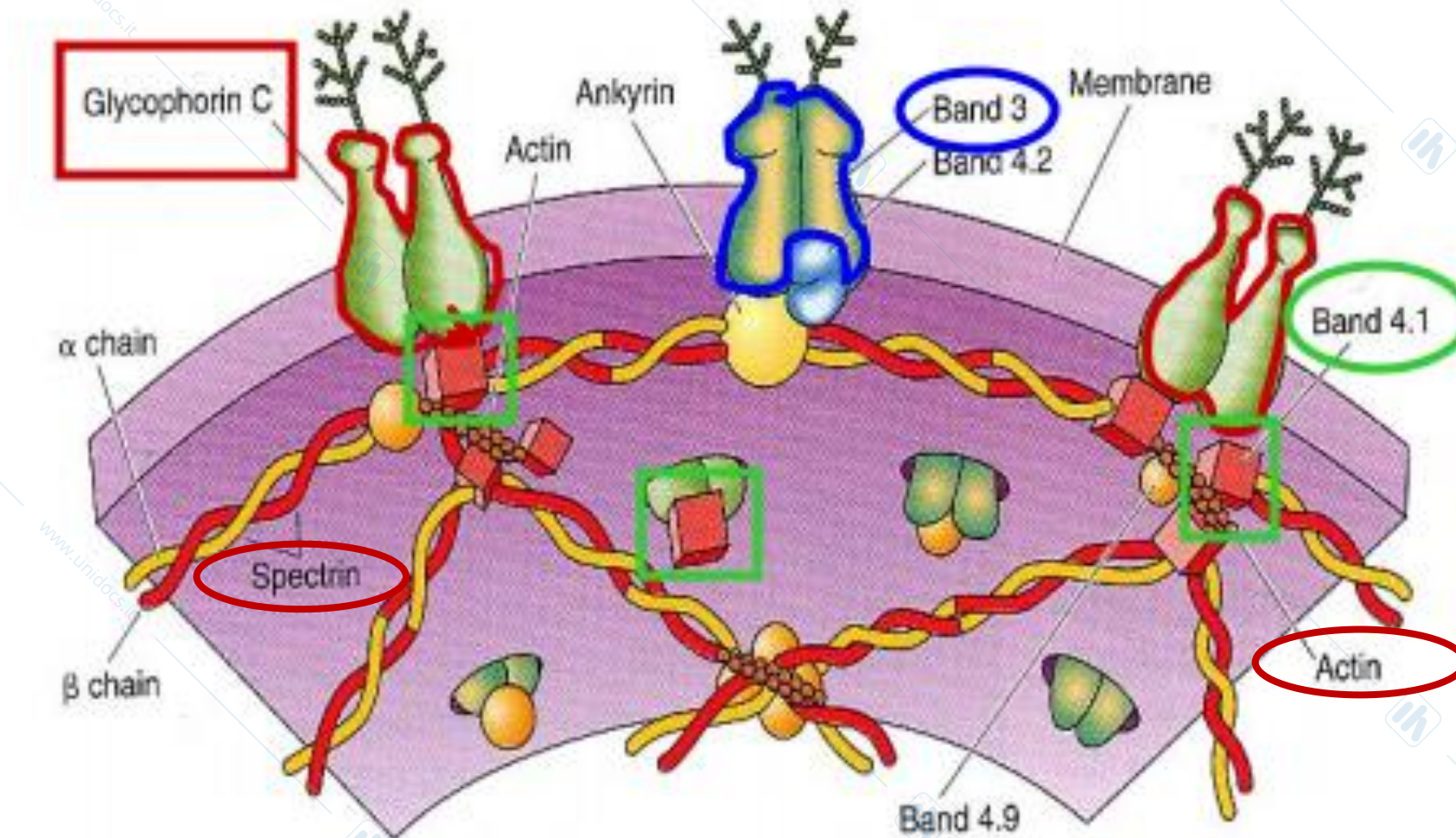
Isotonic



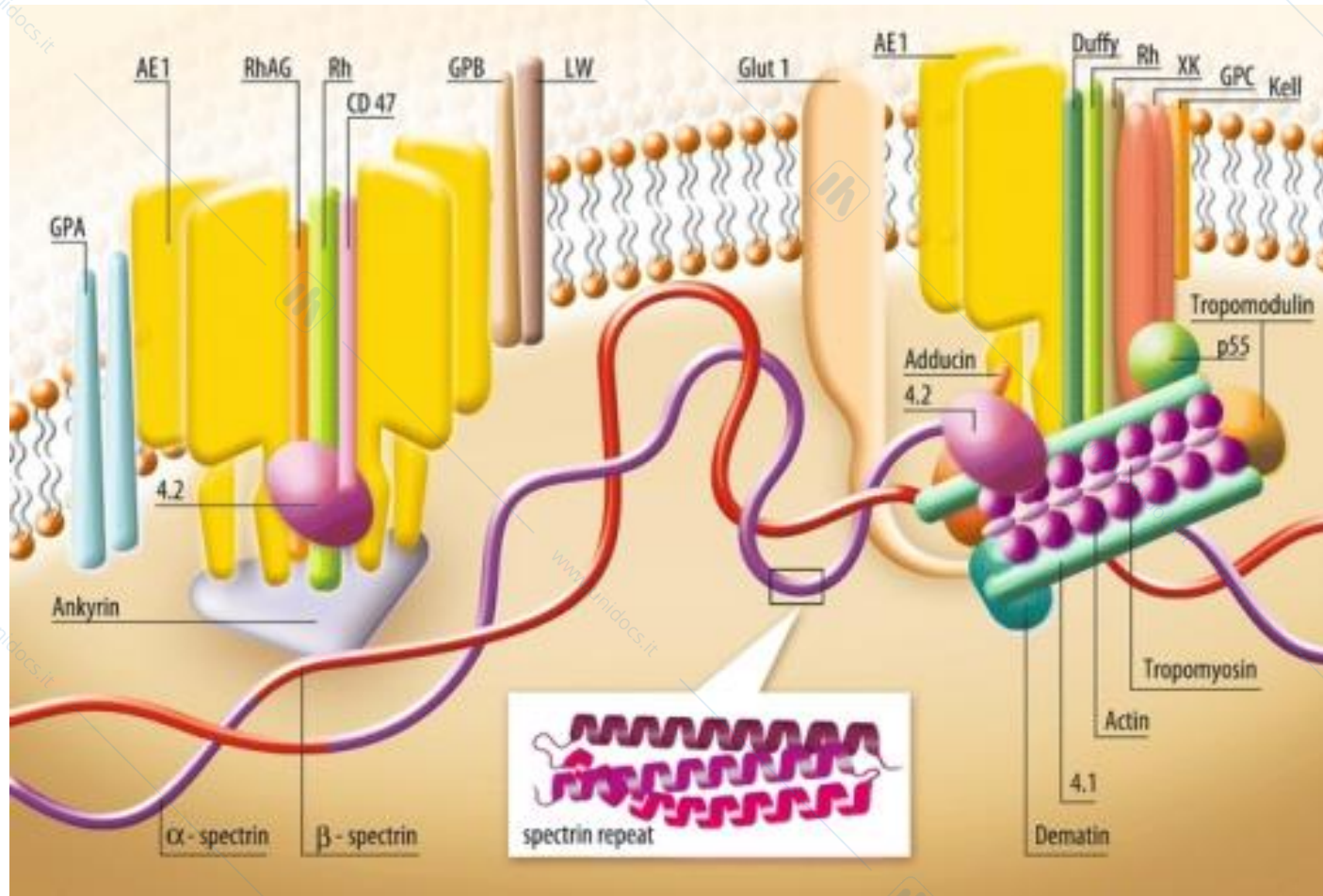
Hypotonic



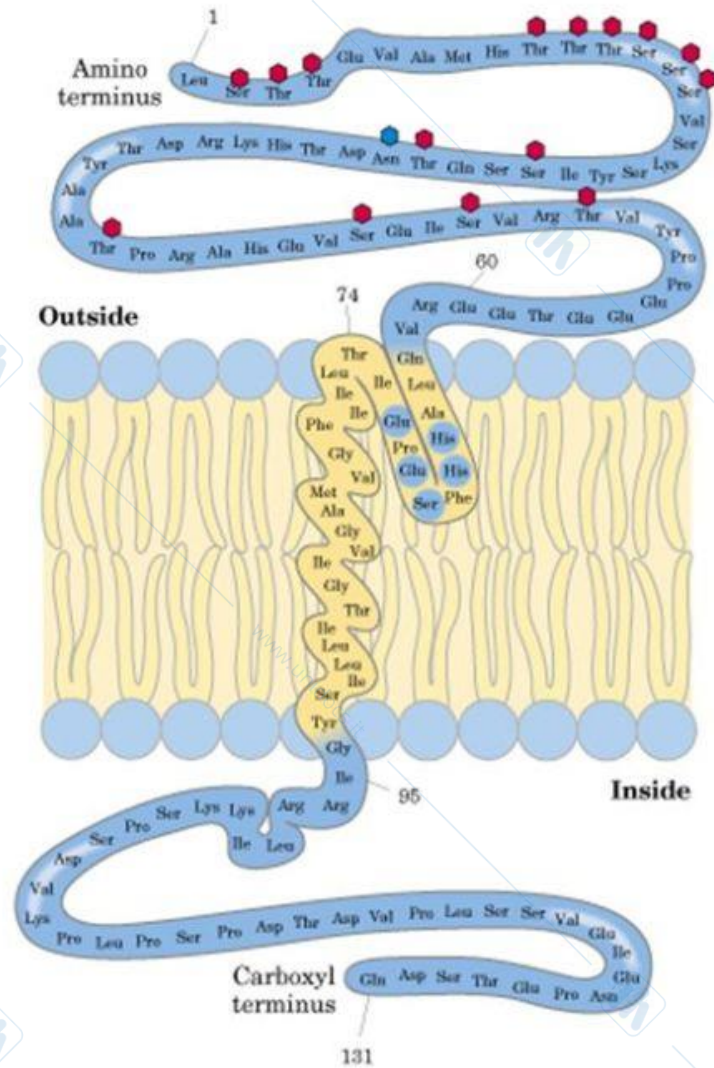
SCHELETRO DI MEMBRANA



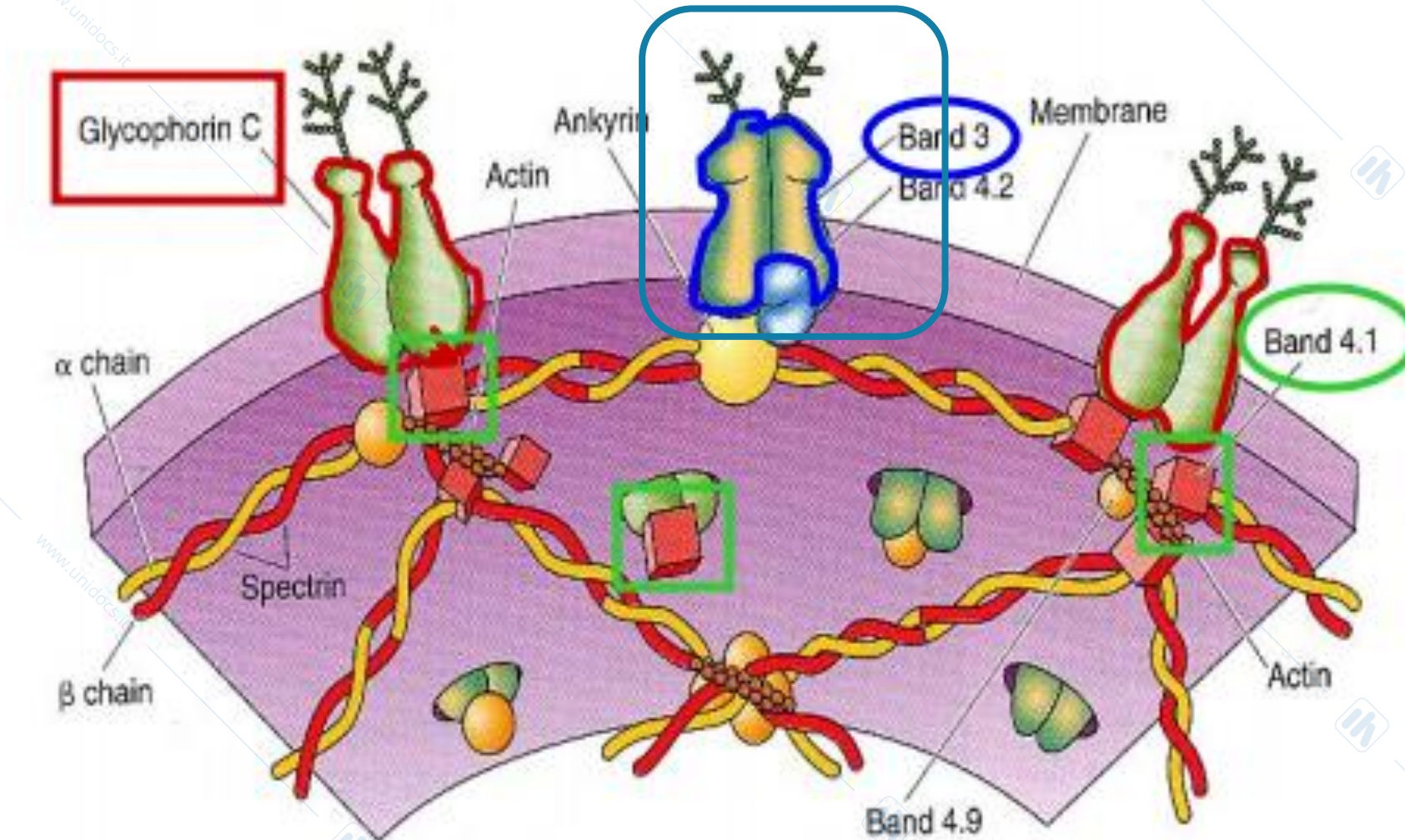
SPECTRINA



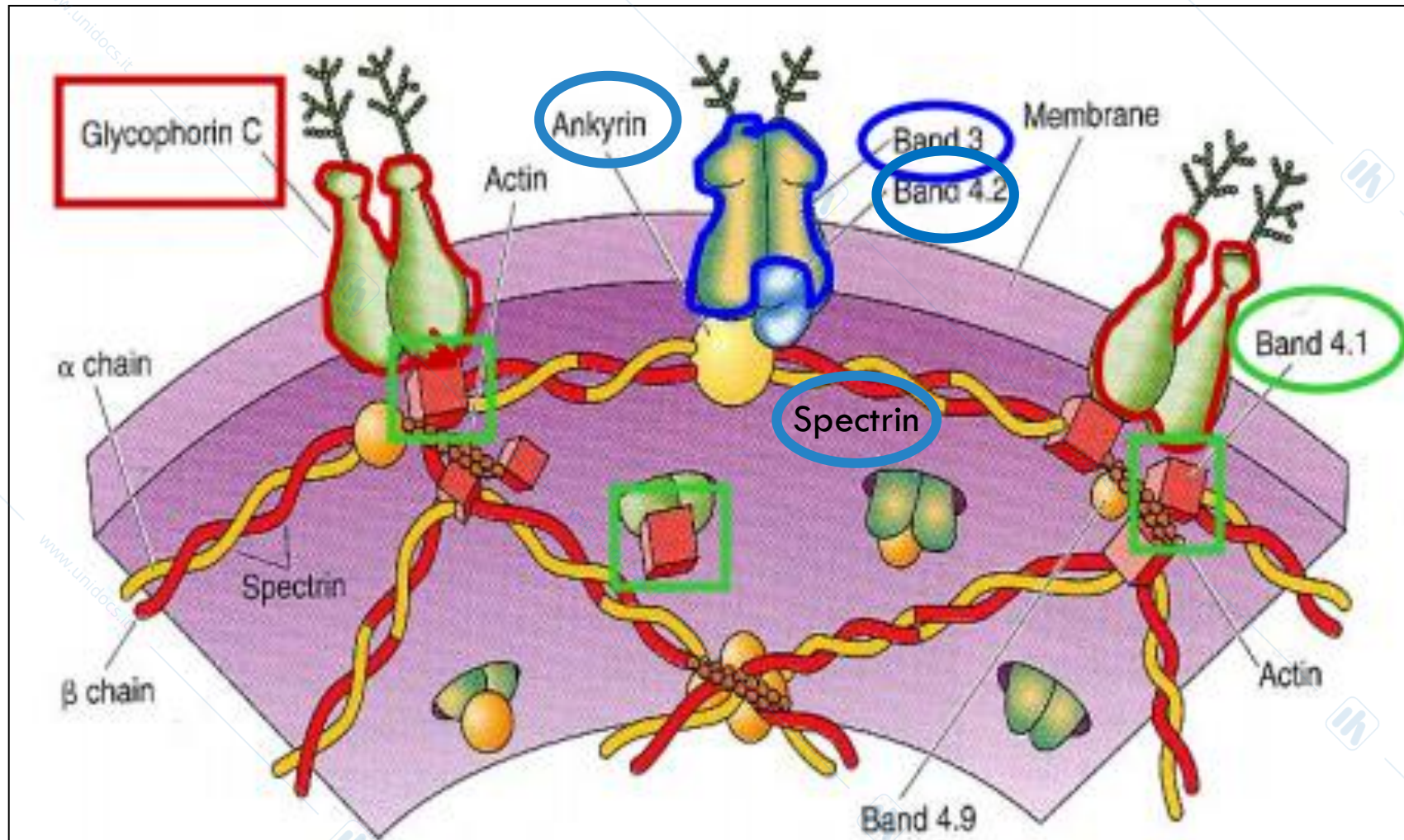
GLICOFORINA C



BANDA 3



COMPLESSO PROTEICO DELL'ANKIRINA



COMPLESSO PROTEICO DELLA BANDA 4.1

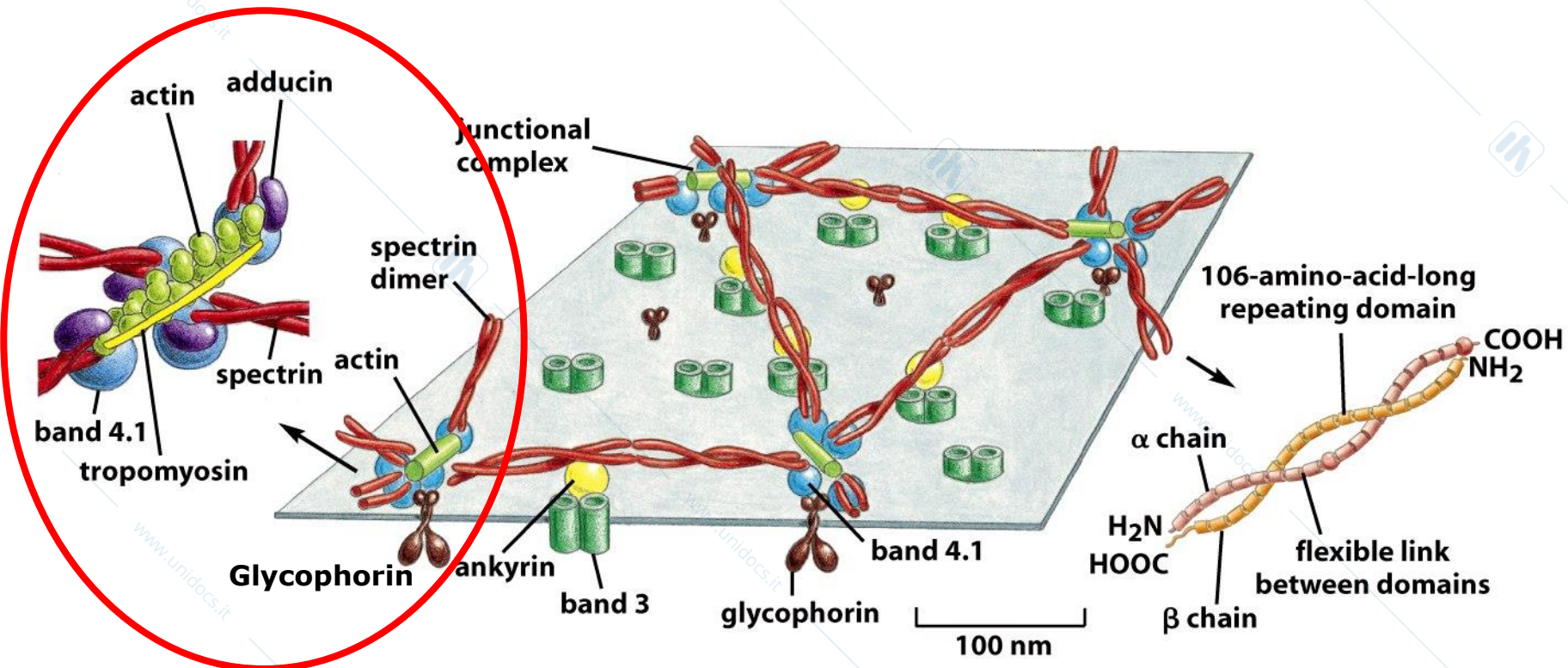


Figure 10-41a *Molecular Biology of the Cell* (© Garland Science 2008)

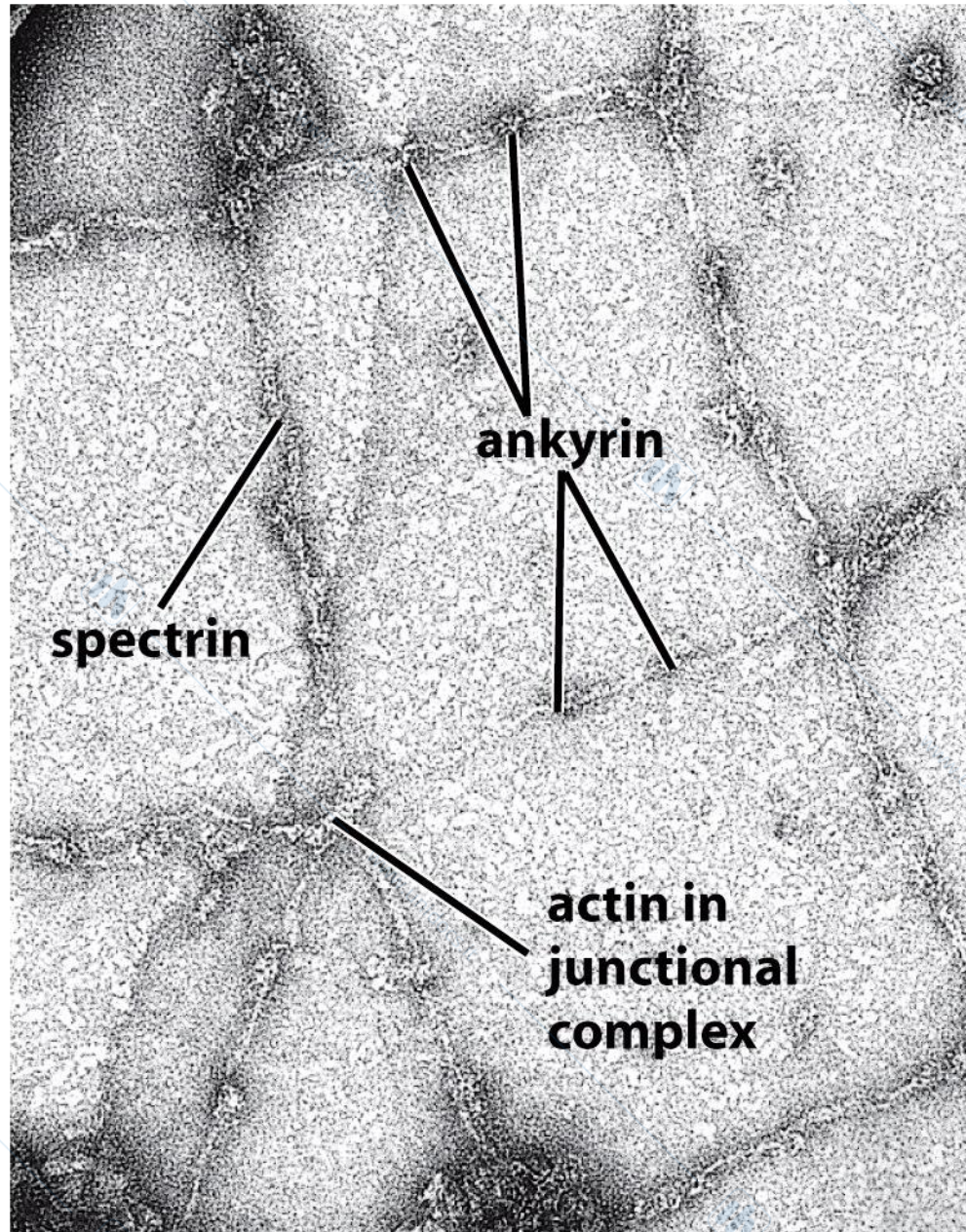
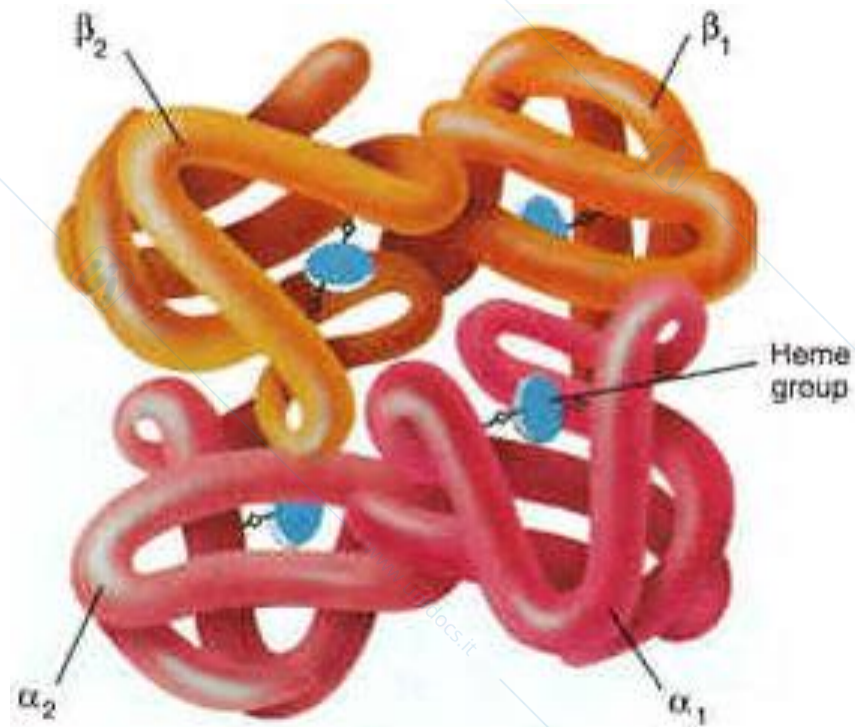
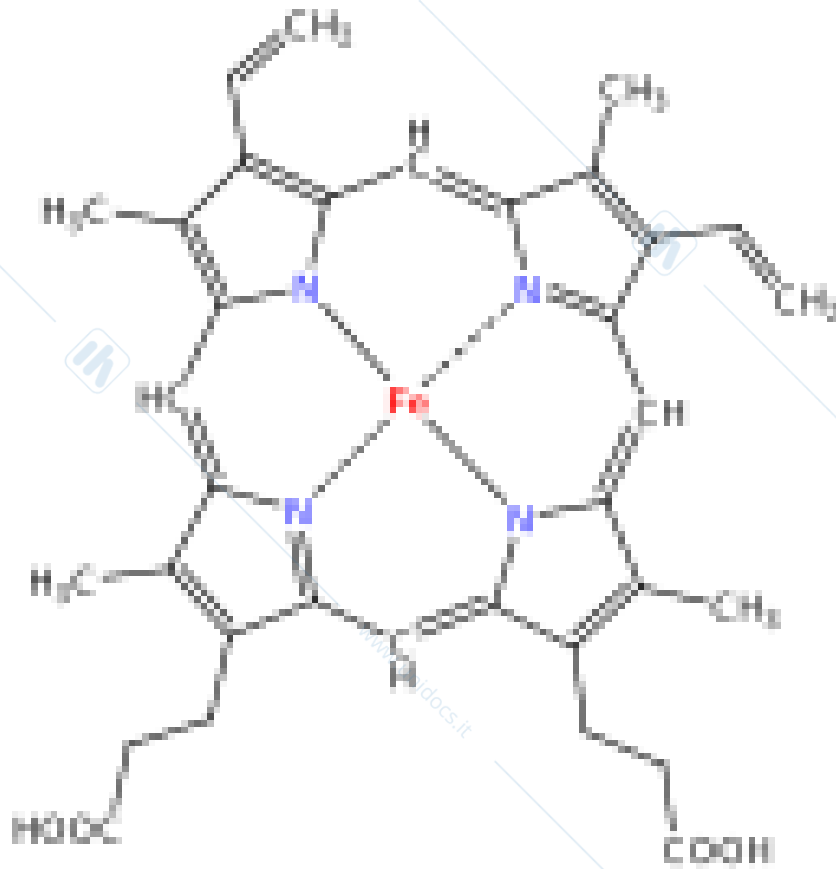


Figure 10-41b *Molecular Biology of the Cell* (© Garland Science 2008)

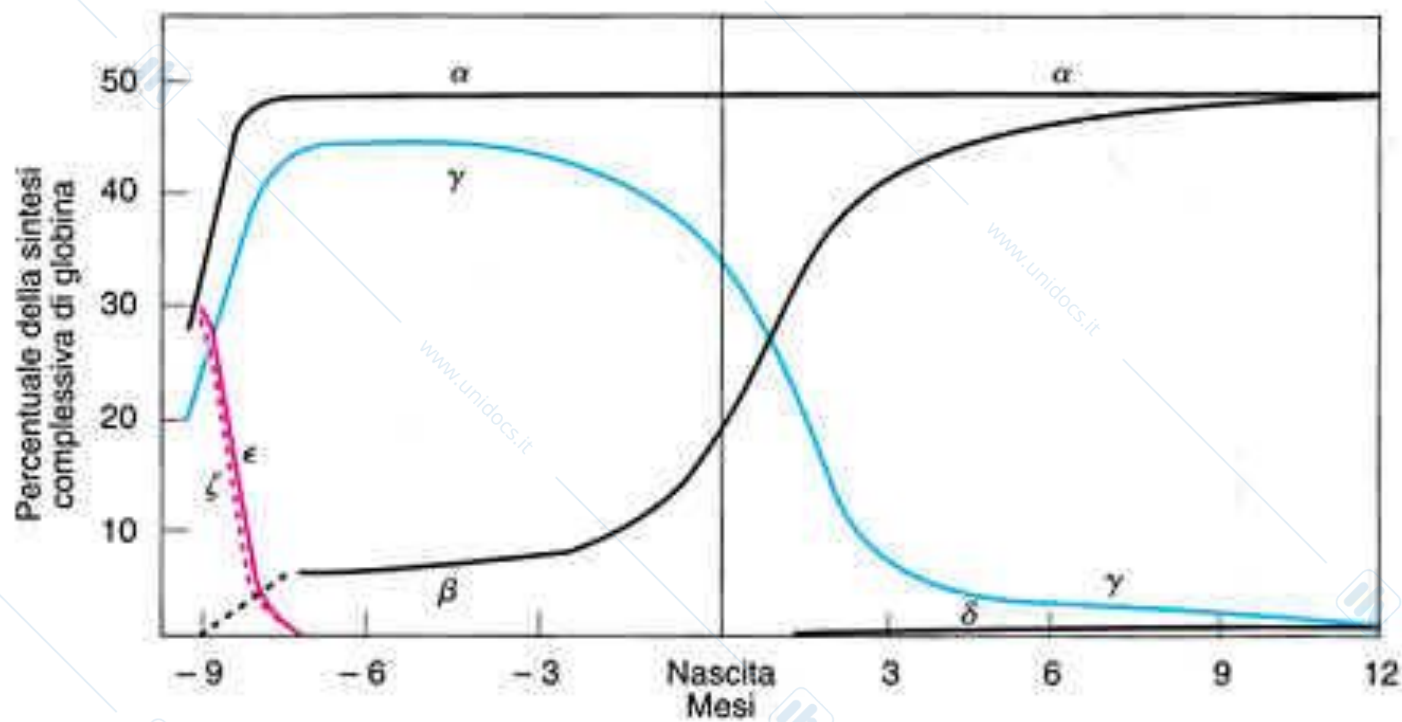
EMOGLOBINA



GRUPPO EME



EMOGLOBINA



Ossiemoglobina (HbO₂)

Desossiemoglobina

Carbossiemoglobina

Metaemoglobina: Fe³⁺ (Fe ferrico, Fe ossidato), o Hb ferrica, forma fisiologicamente non funzionante

ANEMIA A CELLULE FALCIFORMI



TALASSEMIE

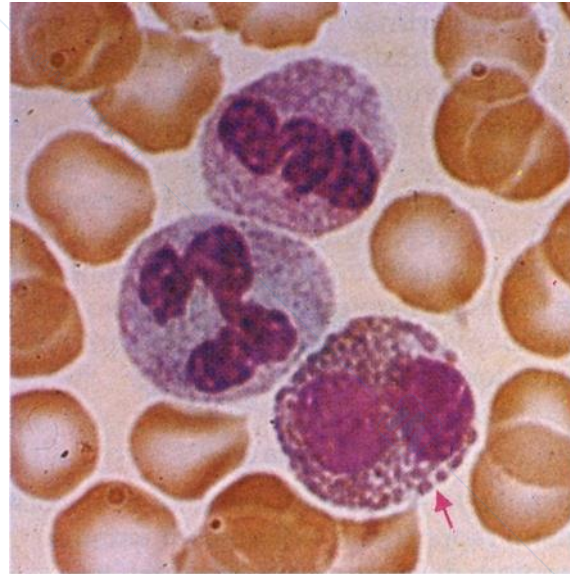
Ridotta o assente sintesi di una o più catene globiniche
Talassemie α , β , γ , δ , $\alpha\beta$

α -talassemia: tetrameri β (Hb4). In omozigosi po' essere letale i nella vita fetale o subito dopo la nascita

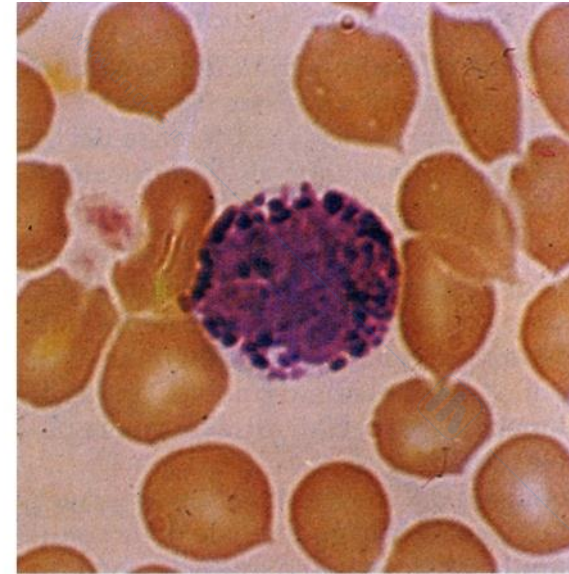
β -talassemia: eccesso di catene α che precipitano nei precursori eritroidi. Talssemia major (mutazione della catena β in omozigosi) morte prematura; talassemia minor (mutazione in eterozigosi)

LEUCOCITI (WBC)

- Linfociti
- Monociti
- Granulociti:
 - Neutrofili
 - Basofili
 - Eosinofili



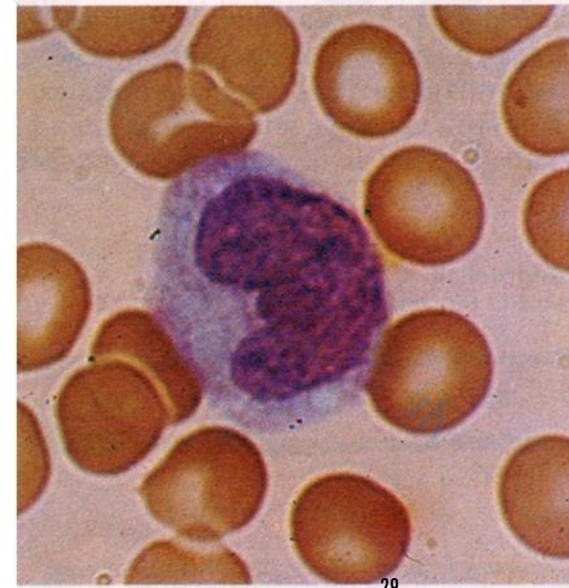
Granulociti neutrofili e granulocito acidofilo (freccia)



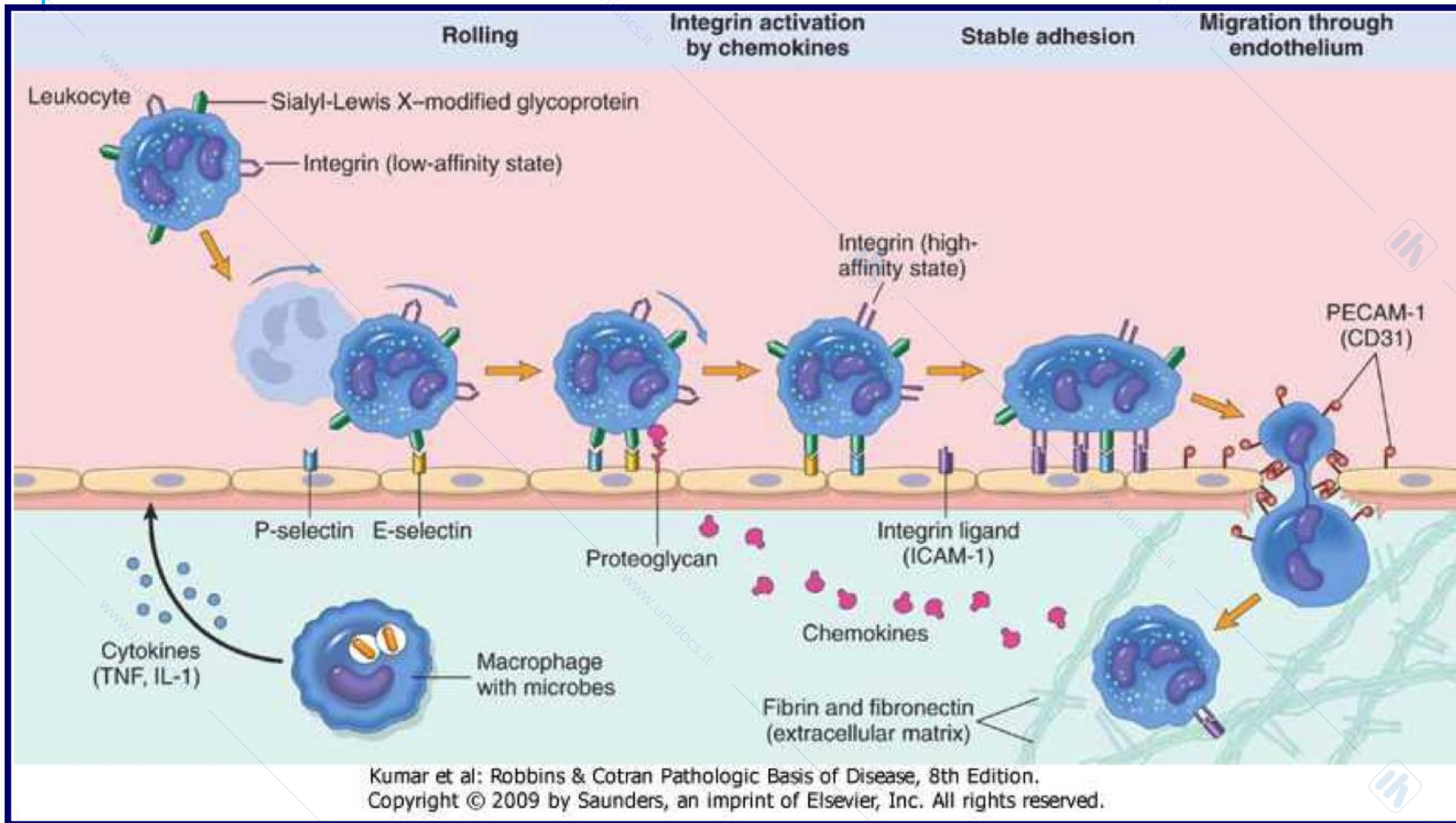
Granulocito basofilo



Linfocito



Monocito



LEUCOCITI

Nella sedimentazione si dispongono tra plasma ed eritrociti: "buffy coat"
($>1\%$)

Formula leucocitaria:

granulociti neutrofili 55-65 %

granulociti eosinofili 0-3%

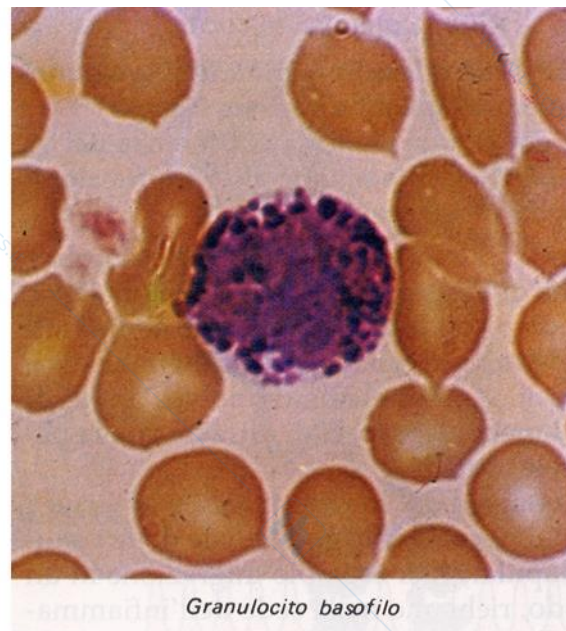
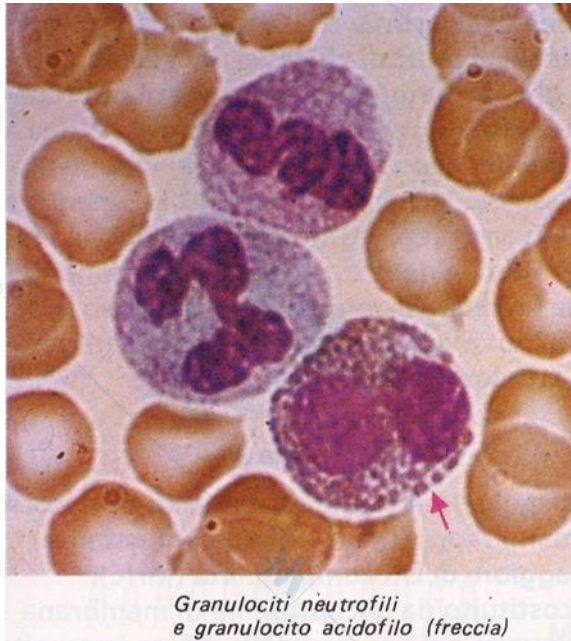
granulociti basofili 0-2 %

linfociti 20-35 %

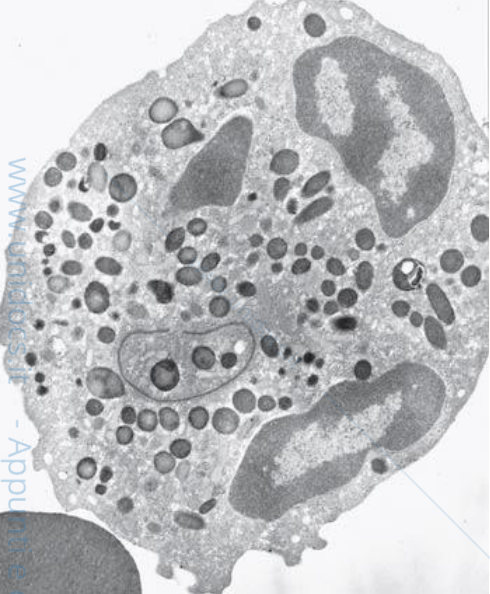
monociti 3 - 7 %

GRANULOCITI O LEUCOCITI POLIMORFONUCLEATI

- Nucleo polisegmentato
- Citoplasma abbondante con granulazioni:
 - G.Eosinofili: eosina tinge i granuli in rosa
 - G.basofili: blu di metilene li tinge in blu
 - G.neutrofili: Sali neutri li colorano in nocciola



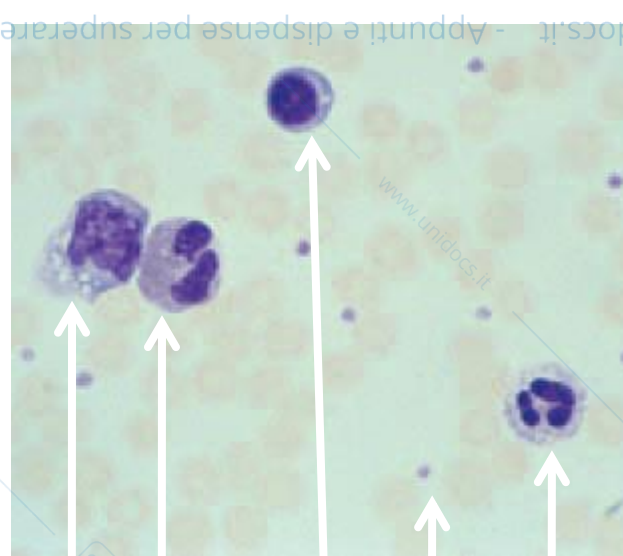
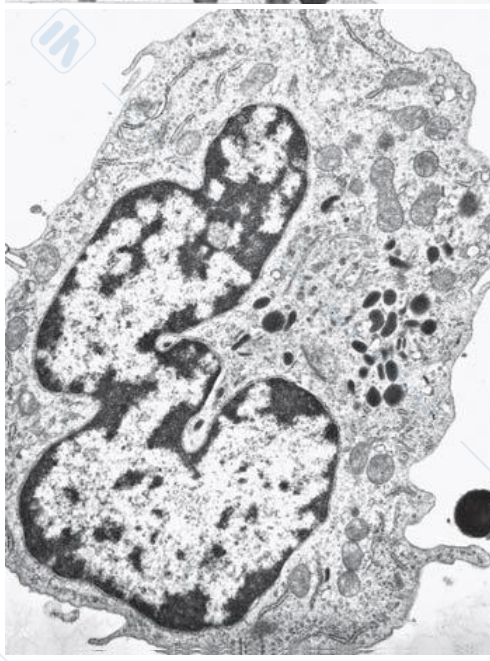
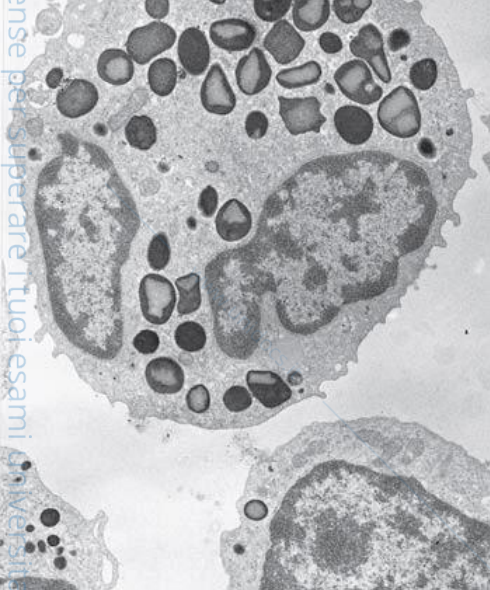
NEUTROFILO



BASOFILI



EOSINOFILO



monocyte
eosinophil
lymphocyte
platelet
neutrophil

Figure 23-37 White blood cells.

here has a different function, which is reflected in the distinctive types of secretory granules and lysosomes it contains. There is only one nucleus per cell, but it has an irregular lobed shape and in (A), (B), and (C) the connections between the lobes are out of the plane of section. (E) A light micrograph of a blood smear stained with the Romanowsky stain, which colors the white blood cells strongly. (A-D, from B.A. Nichols et al., *J. Cell Biol.* 50:498-515, 1971. With permission from The Rockefeller University Press; E, courtesy of David Mason.)

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Granulociti Neutrofili

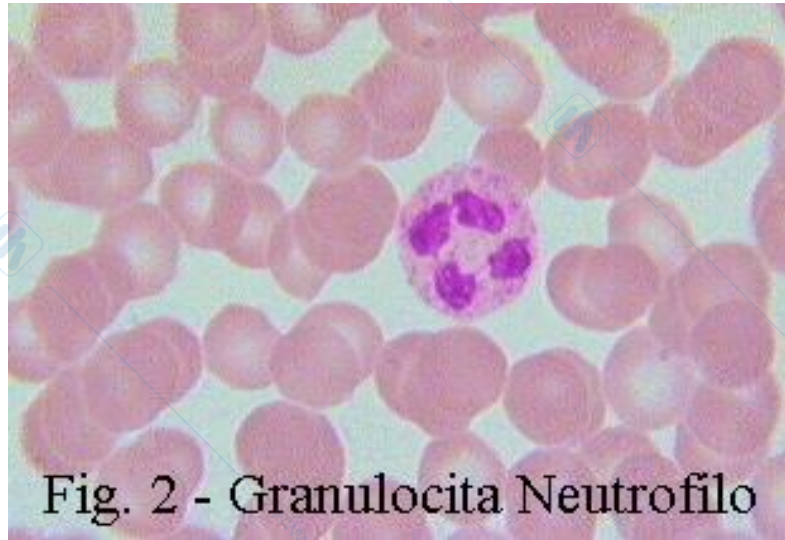
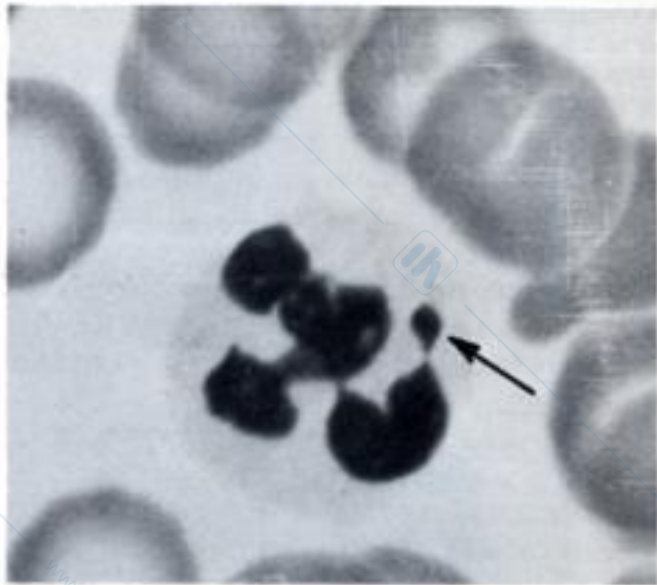
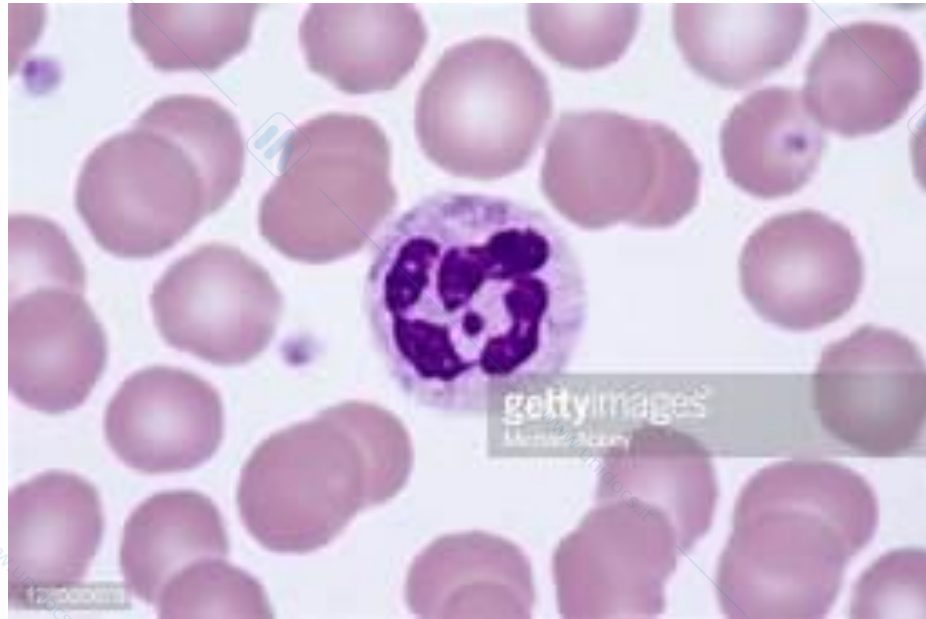


Fig. 2 - Granulocita Neutrofilo

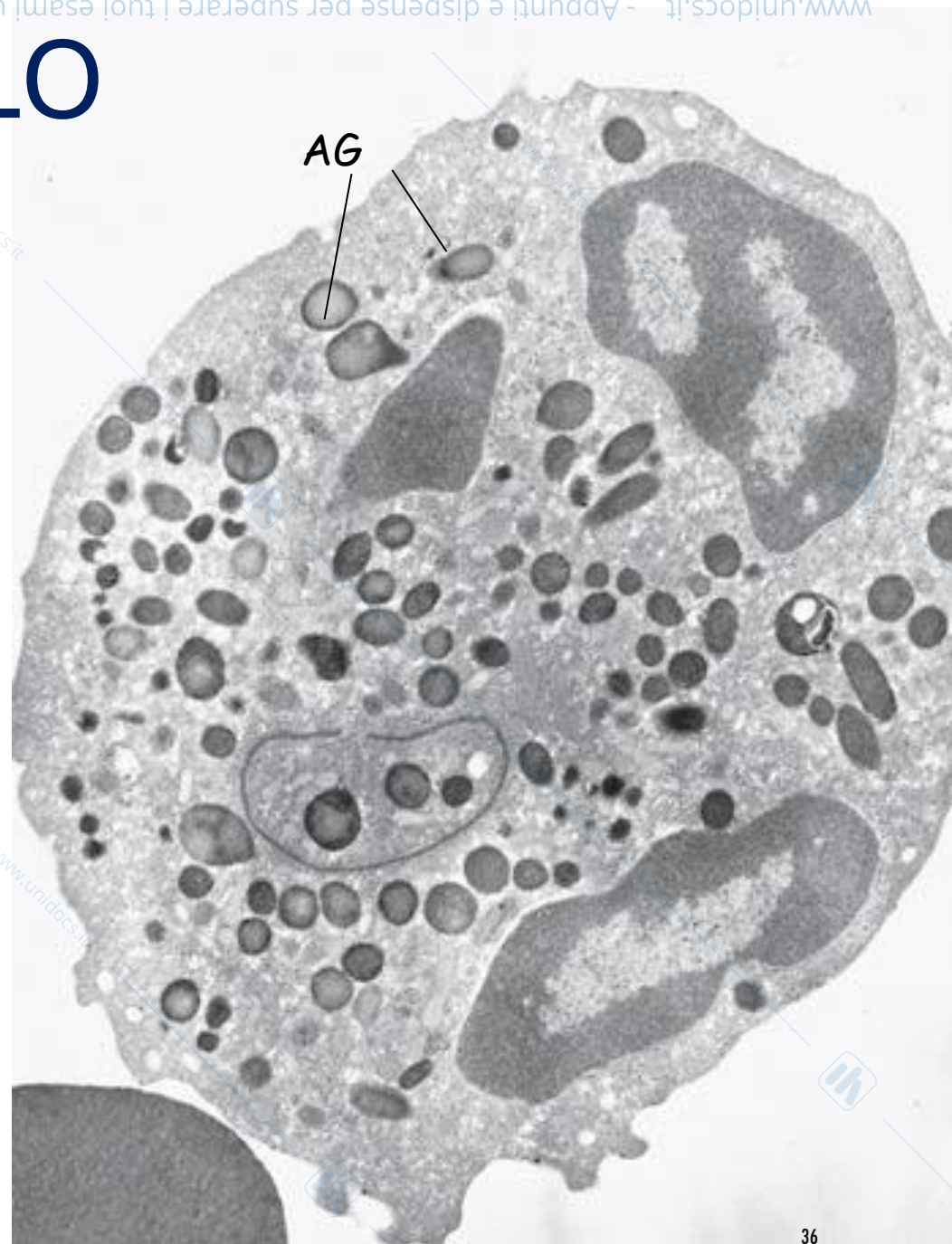
Cromatina nucleare di Barr (eteropicnosi cromosoma X)



Granulocito neutrofilo di sangue umano. È ben evidente (freccia) la cromatina sessuale («drumstick») sporgente da un lobo del nucleo (da U. Mittwoch).



G. NEUTROFILO



GRANULOCITI NEUTROFILI

- ❖ Granuli primari o Azzurrofilii:
- ❖ Granuli secondari o specifici (80%)
- ❖ Granuli terziari

Ruolo difensivo dei Neutrofili

❖ **Richiamo nella sede di infezione da fattori chemiotattici:**

C_{5a} , C_{3b} , C_{5-6-7}

Fibrinopeptide B, plasmina, callicreina,

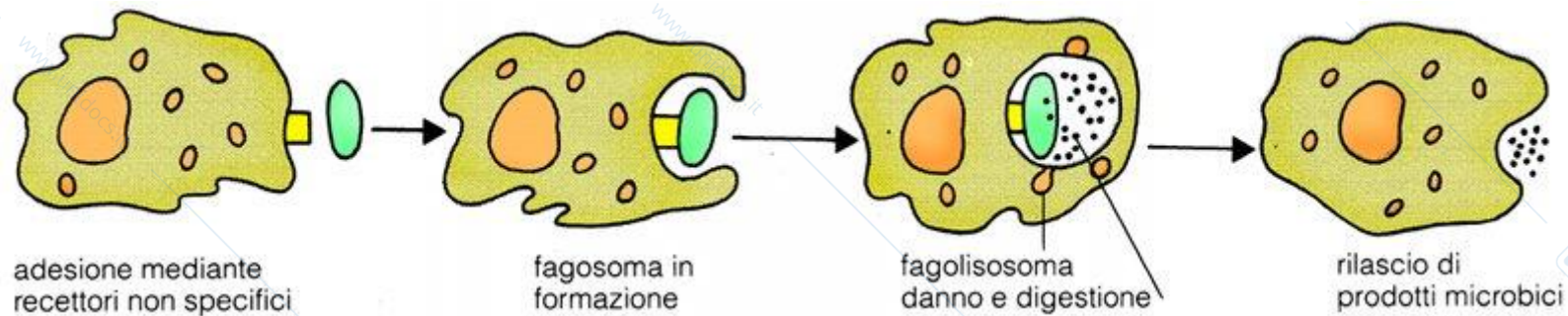
Prodotti di derivazione batterica

Prodotti liberati da monociti, macrofagi e linfociti

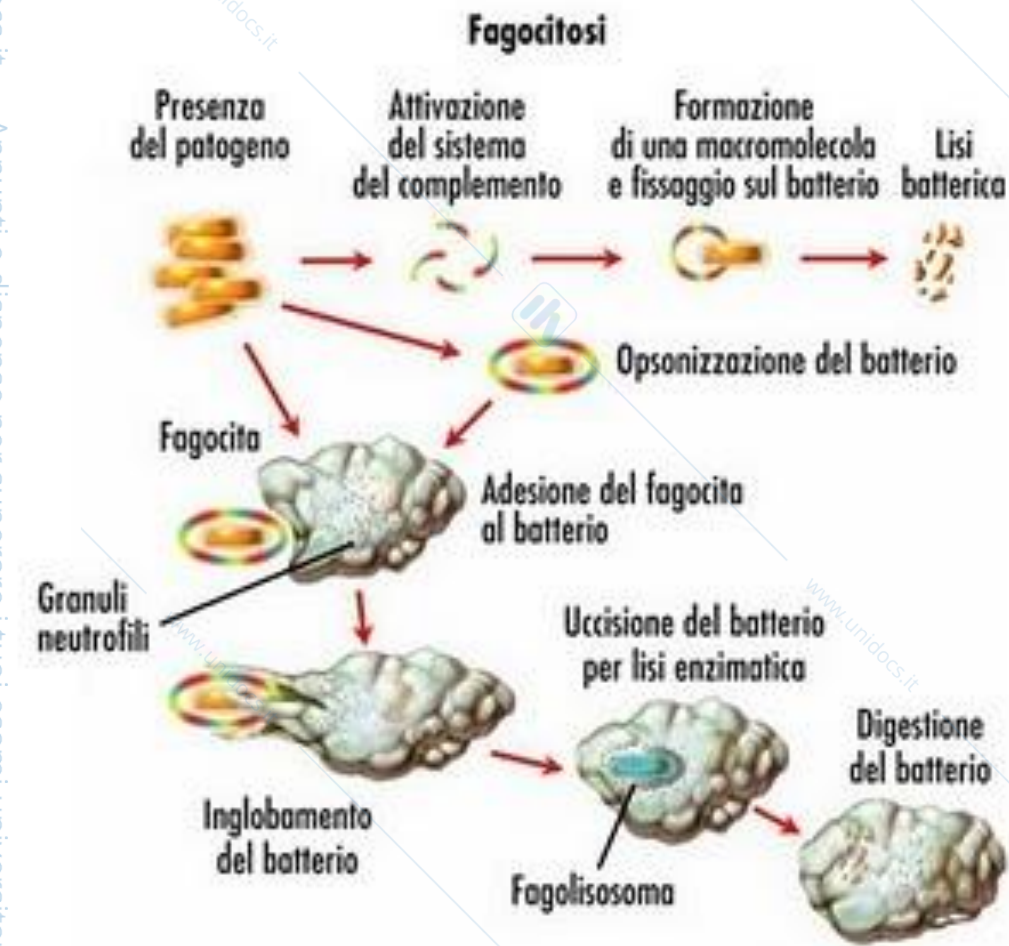
❖ **Migrazione verso il luogo di infezione**

Ruolo difensivo dei Neutrofili

- ❖ Riconoscimento di particelle estranee opsonizzate (opsonine: anticorpi IgG e fattori del complemento C₃b).
- ❖ Attivazione della fagocitosi
- ❖ Fase di degranulazione



RUOLO DIFENSIVO DEI NEUTROFILI



Granulociti Eosinofili

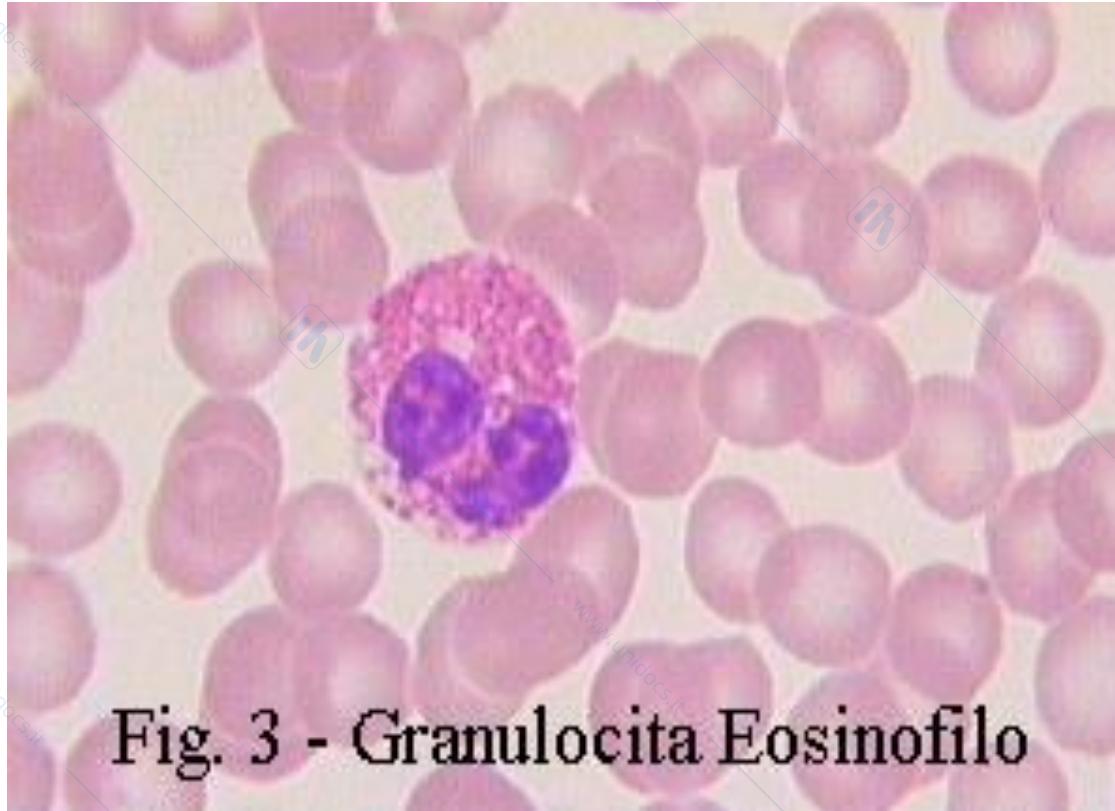


Fig. 3 - Granulocita Eosinofilo

Granulociti Eosinofili



GRANULOCITI BASOFILI

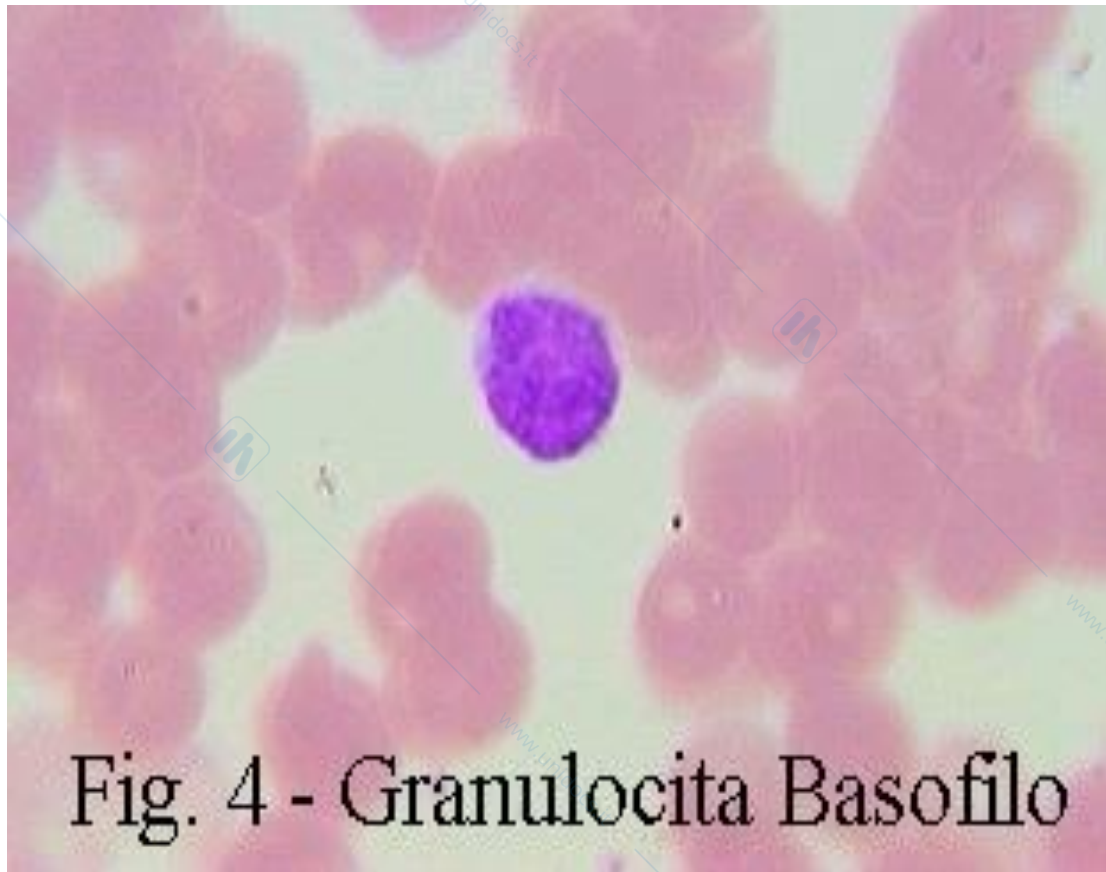


Fig. 4 - Granulocita Basofilo

Granulociti Basofili

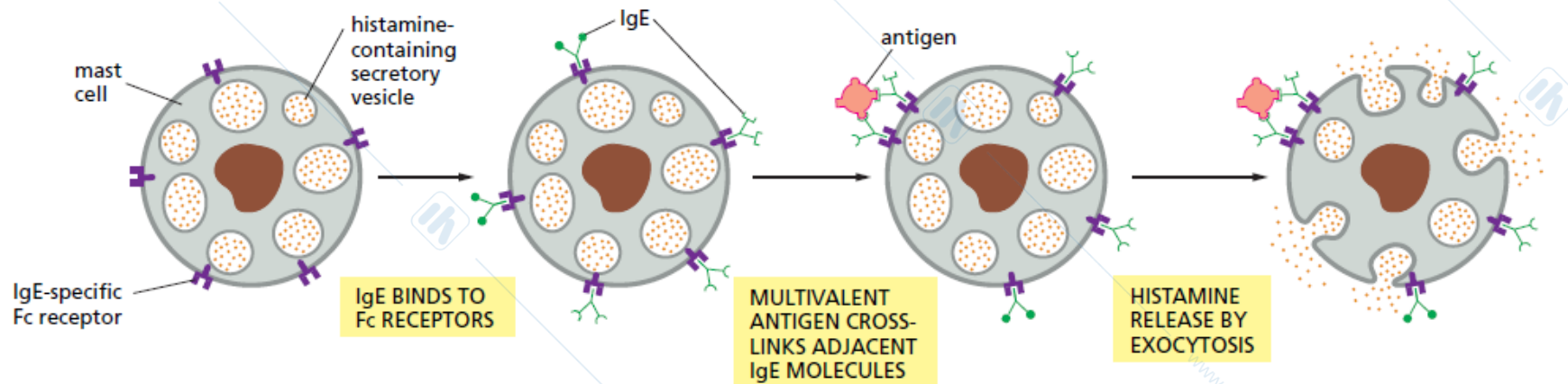
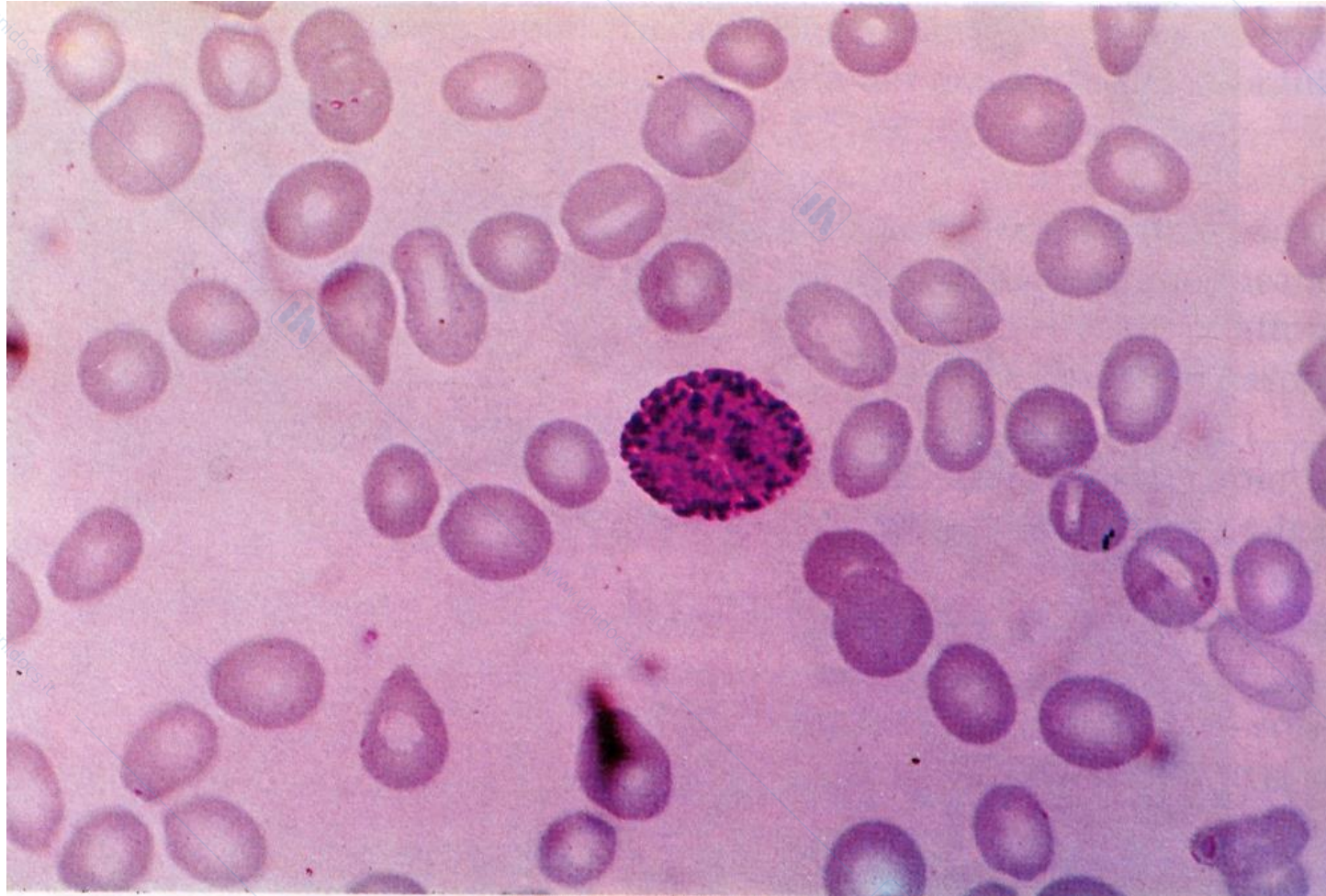


Figure 25–27 The role of IgE in histamine secretion by mast cells. A mast cell (or a basophil) binds IgE molecules after they are secreted by effector B cells. The soluble IgE antibodies bind to Fc receptor proteins on the mast cell surface that specifically recognize the Fc region of these antibodies. The bound IgE molecules serve as cell-surface receptors for antigen. Thus, unlike B cells, each mast cell (and basophil) has a set of cell-surface antibodies with a wide variety of antigen-binding sites. When an antigen molecule binds to these membrane-bound IgE antibodies so as to cross-link them to their neighbors, it signals the mast cell to release its histamine and other local mediators by exocytosis.

Granulociti Basofili



MONOCITI

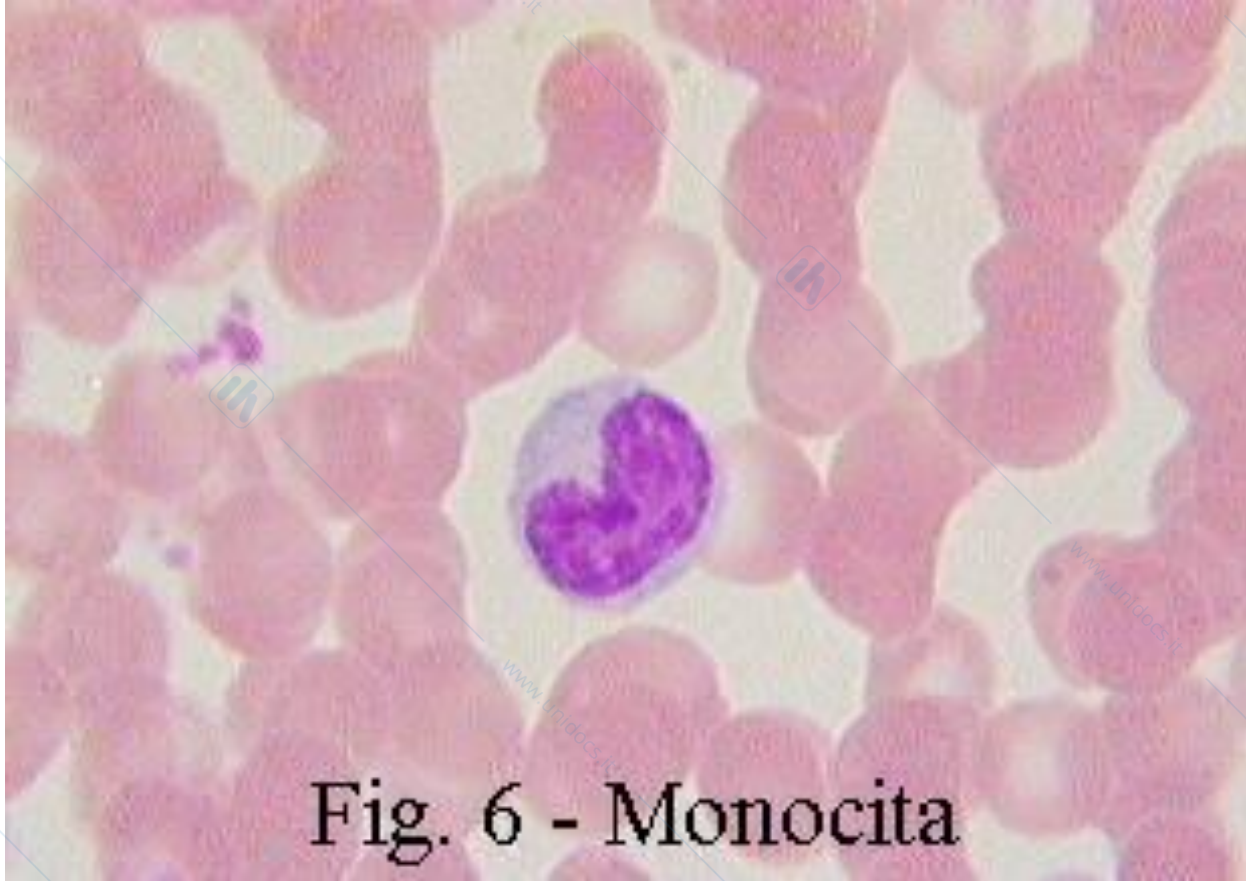
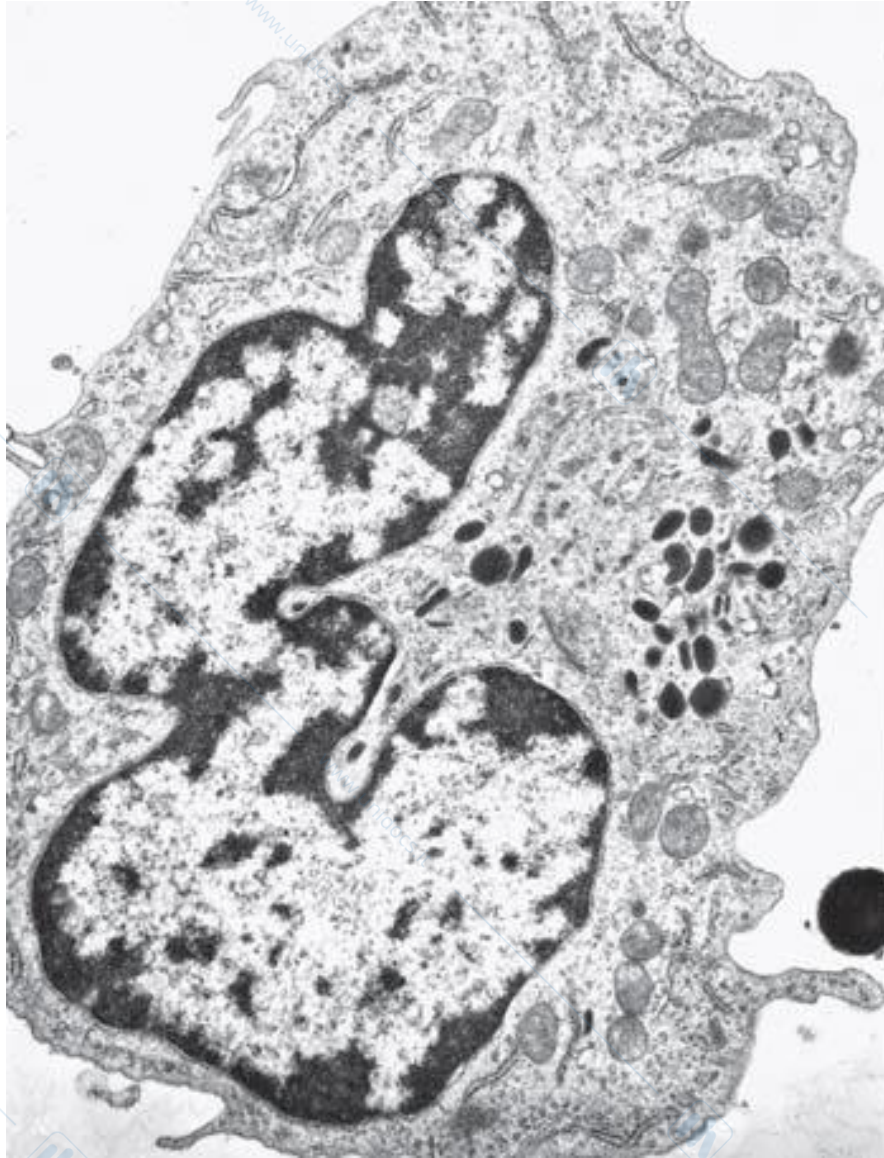


Fig. 6 - Monocita

MONOCITI



LINFOCITI

Piccole cellule con nucleo compatto che occupa quasi tutto il volume cellulare.

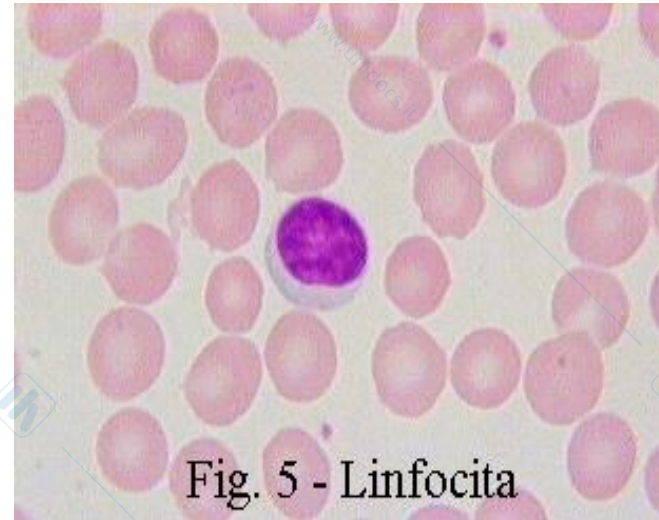
Nel sangue, i linfociti rappresentano il 20-35% di tutti i leucociti. Si trovano anche nella linfa e nei tessuti

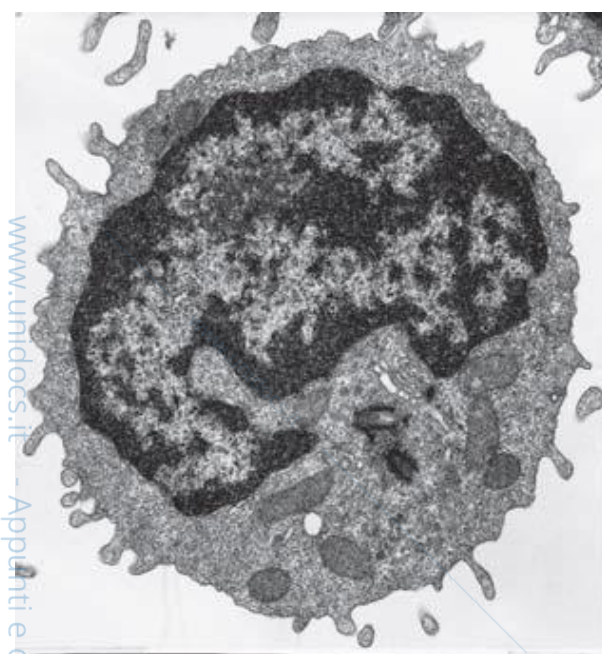
Marcatore linfoide: CD34

Linfociti T (60-80%)

Linfociti B (5-10%)

Cellule NK (5-20%)

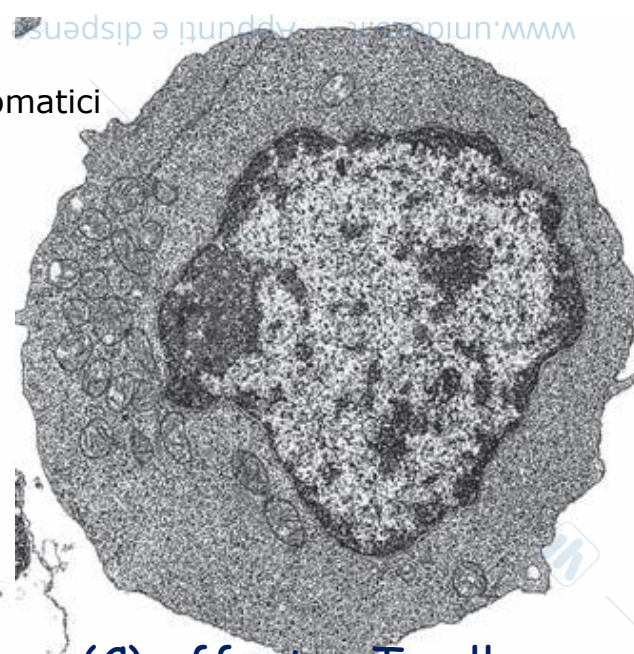




(A) resting T or B cell



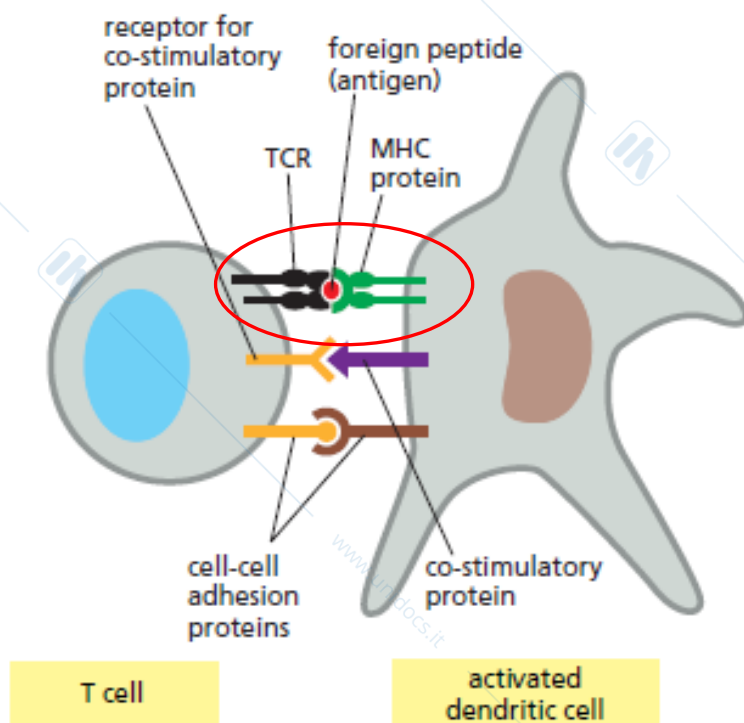
(B) effector B cell (plasma cell)



(C) effector T cell

Figure 25-7 Electron micrographs of resting and effector lymphocytes. (A) This resting lymphocyte could be either a T cell or a B cell, as these cells are difficult to distinguish morphologically until they have been activated to become effector cells. (B) An effector B cell (a plasma cell). It is filled with an extensive rough endoplasmic reticulum (ER), which is distended with antibody molecules. (C) An effector T cell, which has relatively little rough ER but is filled with free ribosomes. The three cells are shown at the same magnification. (A, courtesy of Dorothy Zucker-Franklin; B, courtesy of Carlo Grossi; A and B, from D. Zucker-Franklin et al., *Atlas of Blood Cells: Function and Pathology*, 2nd ed. Milan, Italy: Edi. Ermes, 1988; C, courtesy of Stefanello de Petris.)

LINFOCITI T



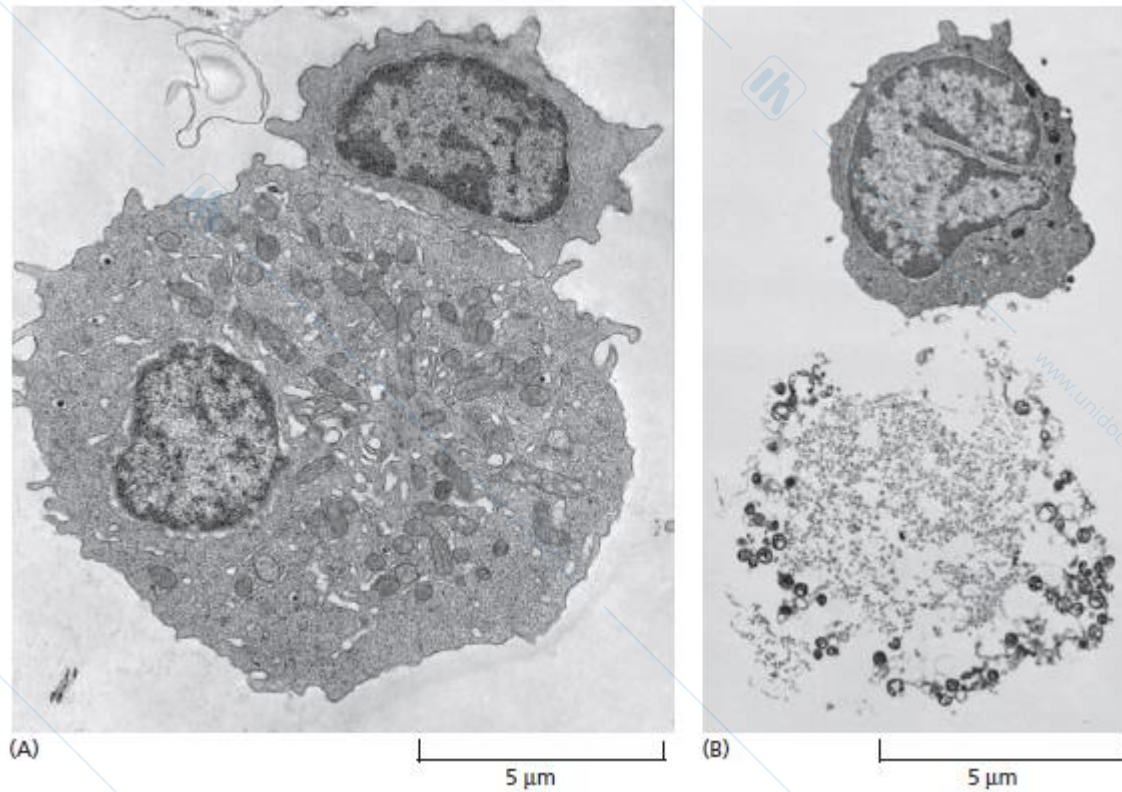
RECETTORI DEI LINFOCITI T

Table 25-3 Some Accessory Proteins on the Surface of T Cells

PROTEIN*	SUPERFAMILY	EXPRESSED ON	LIGAND ON TARGET CELL	FUNCTIONS
CD3 complex	Ig (except for ζ)	all T cells	—	helps transduce signal when antigen-MHC complexes bind to TCRs; helps transport TCRs to cell surface
CD4	Ig	helper T cells, regulatory T cells	class II MHC	promotes adhesion to dendritic cells and target cells; signals T cell
CD8	Ig	cytotoxic T cells	class I MHC	promotes adhesion to dendritic cells and infected target cells; signals T cell
CD28	Ig	most T cells	B7 proteins (CD80 and CD86)	helps activate T cells
CTLA4	Ig	activated T cells	B7 proteins (CD80 and CD86)	inhibits T cell activation
CD40 ligand	Fas ligand family	effector helper T cells	CD40	co-stimulatory protein that helps activate macrophages, B cells, and dendritic cells

*CD stands for cluster of differentiation, as each of the CD proteins was originally defined as a blood cell "differentiation antigen" recognized by multiple monoclonal antibodies. Their identification depended on large-scale collaborative studies in which hundreds of such antibodies, generated in many laboratories, were compared and found to consist of relatively few groups (or "clusters"), each recognizing a single cell-surface protein. Since these initial studies, however, more than 240 CD proteins have been identified.

LINFOCITI T CITOTOSSICI



LINFOCITI T CITOTOSSICI

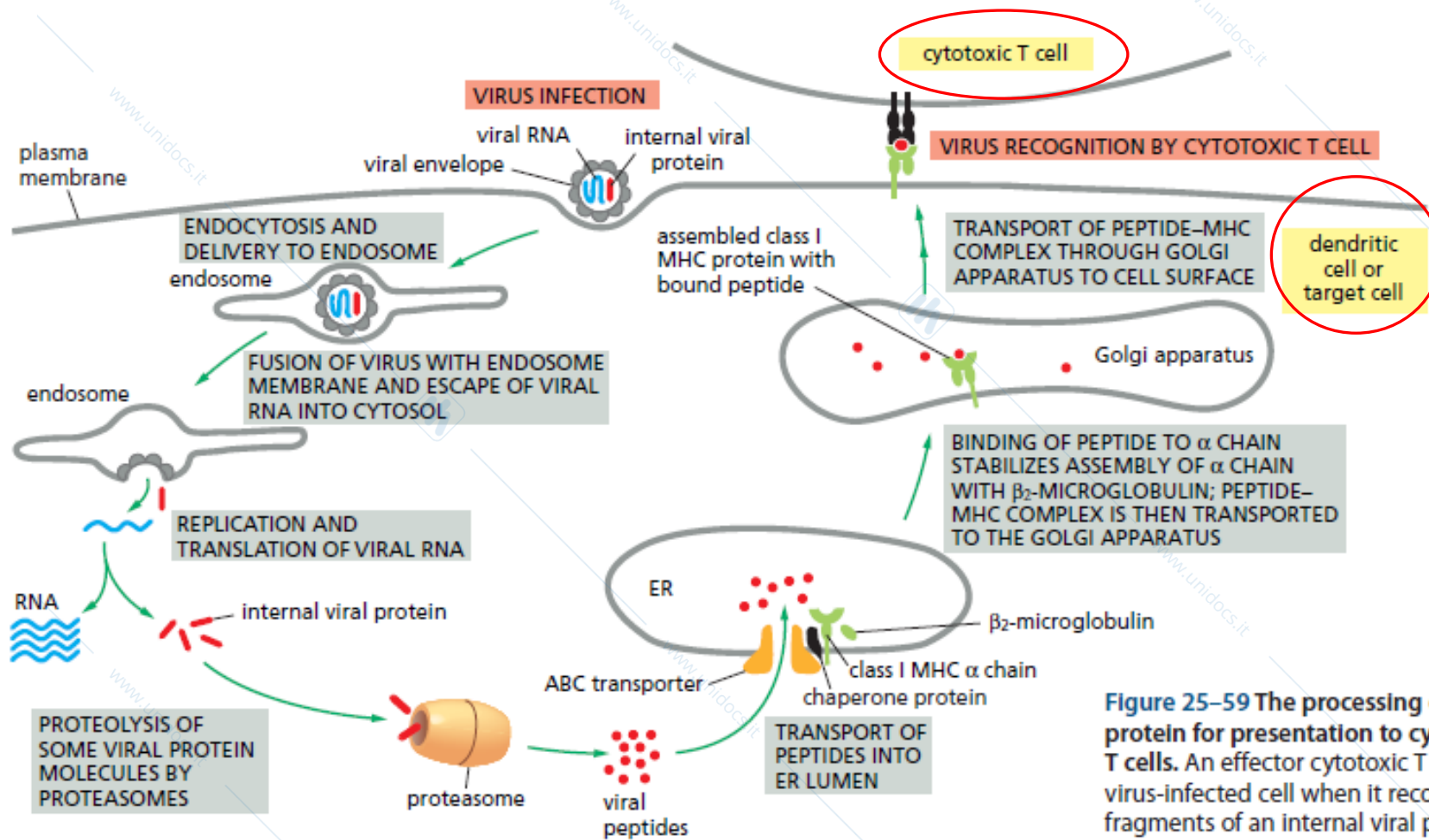


Figure 25-59 The processing of a viral protein for presentation to cytotoxic T cells. An effector cytotoxic T cell kills a virus-infected cell when it recognizes fragments of an internal viral protein bound to class I MHC proteins on the cell surface.

Trasportatore ABC superficie del RE, proteine chaperon aiutano il folding delle MHC

LINFOCITI T CITOTOSSICI

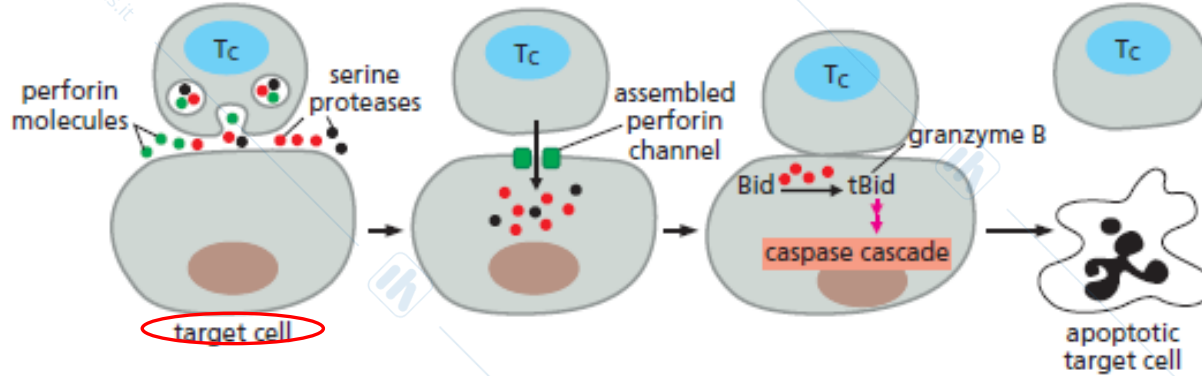
Rilascio per esocitosi di perforina e di enzimi proteolitici

La perforina si assembla in canali transmembrana, attraverso i quali passano gli enzimi proteolitici

Granzima B, attiva una proteina proapoptotica: Bid

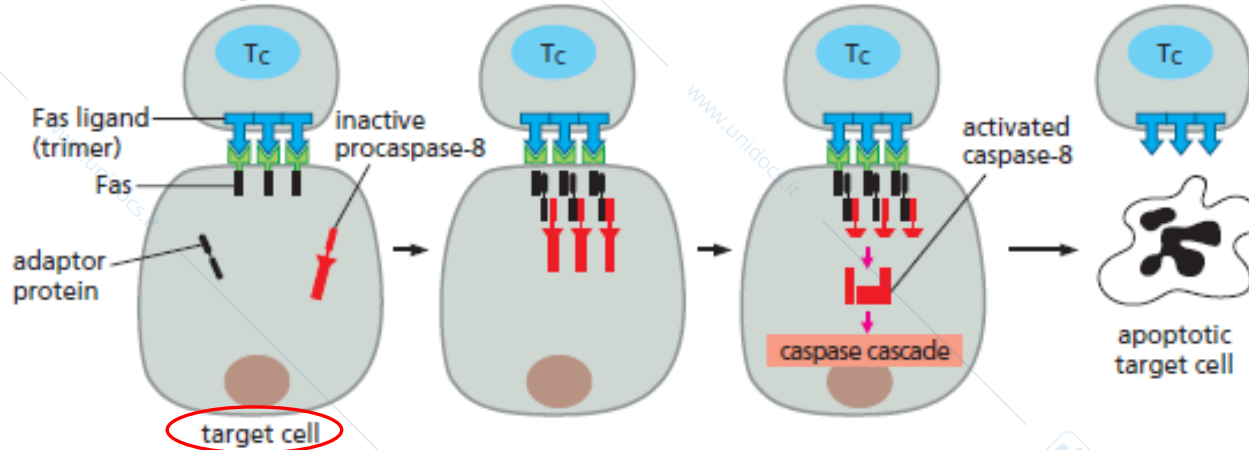
A Perforin-dependent killing

effector cytotoxic T cell

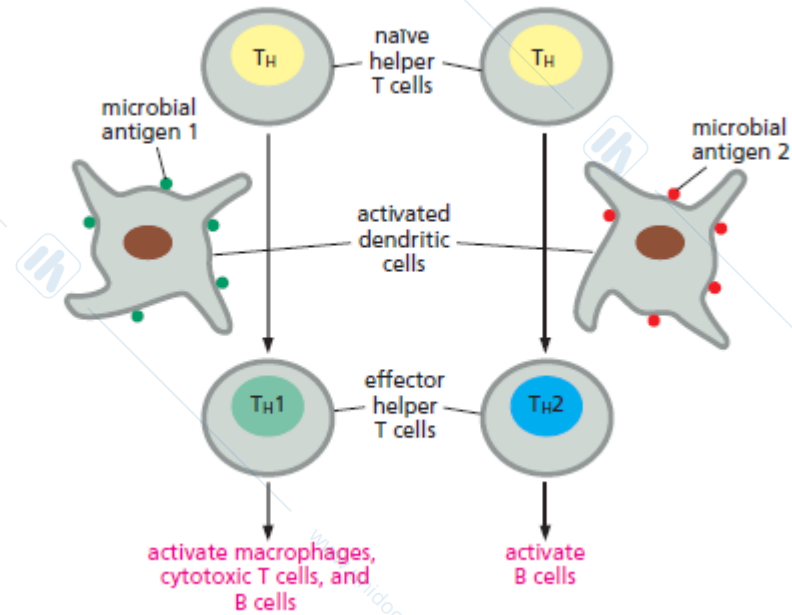


B Fas-dependent killing

effector cytotoxic T cell



LINFOCITI T HELPER



LINFOCITI T HELPER

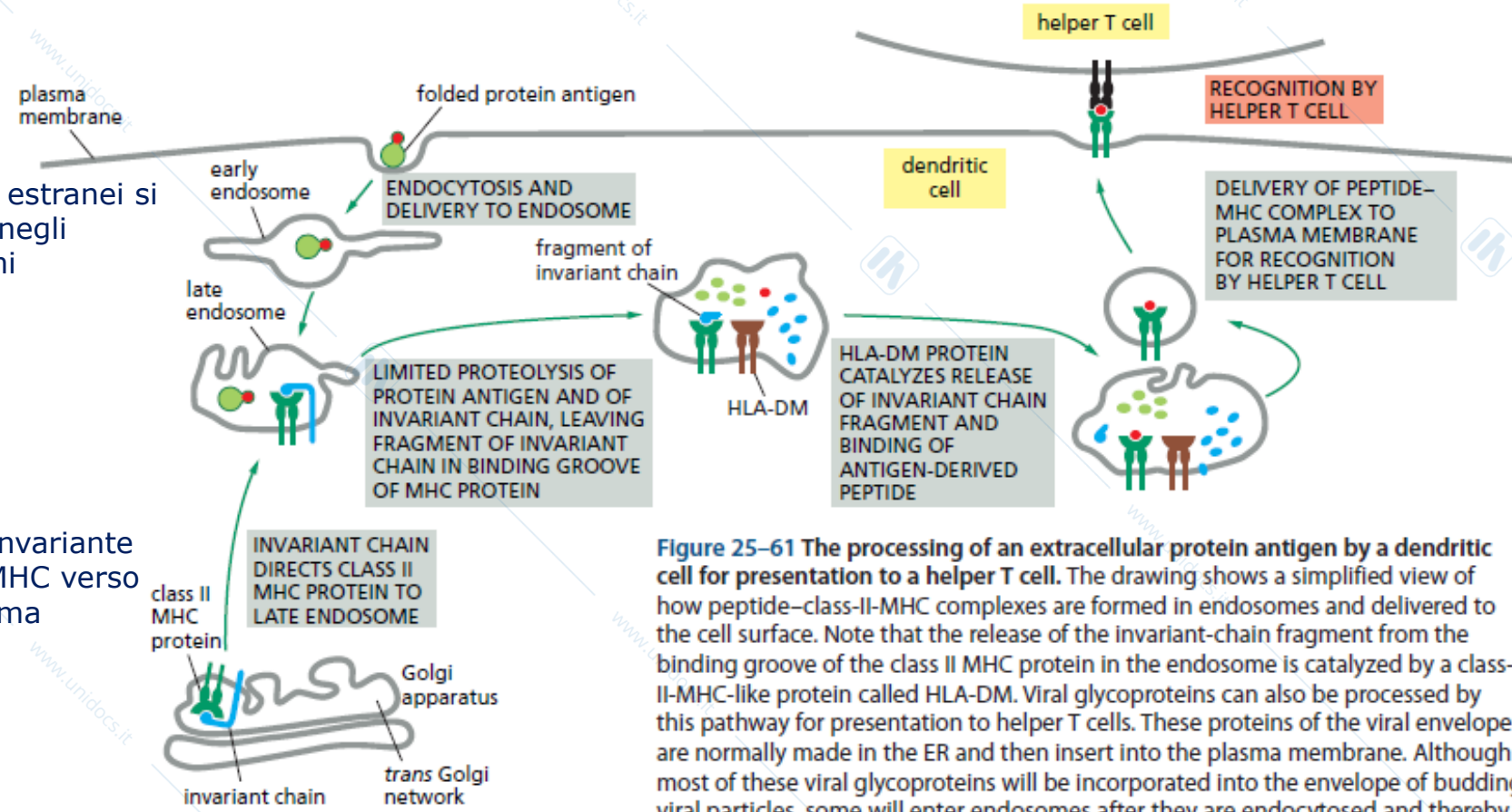


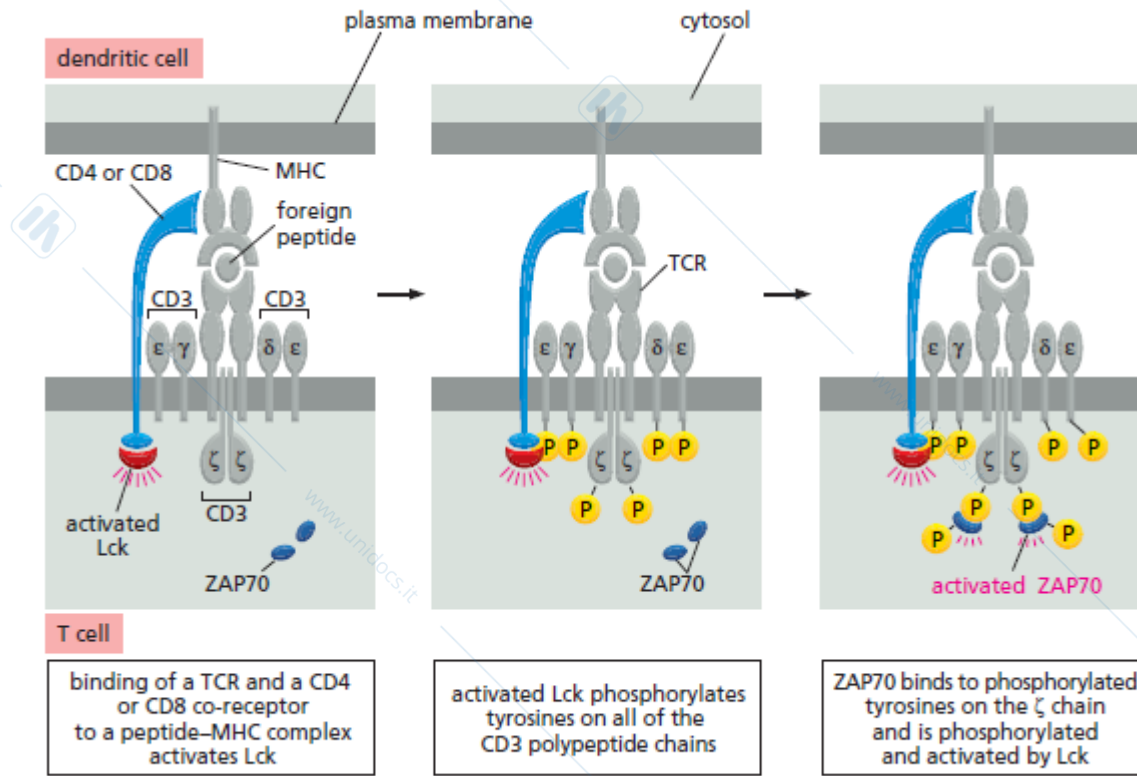
Figure 25-61 The processing of an extracellular protein antigen by a dendritic cell for presentation to a helper T cell. The drawing shows a simplified view of how peptide-class-II-MHC complexes are formed in endosomes and delivered to the cell surface. Note that the release of the invariant-chain fragment from the binding groove of the class II MHC protein in the endosome is catalyzed by a class-II-MHC-like protein called HLA-DM. Viral glycoproteins can also be processed by this pathway for presentation to helper T cells. These proteins of the viral envelope are normally made in the ER and then insert into the plasma membrane. Although most of these viral glycoproteins will be incorporated into the envelope of budding viral particles, some will enter endosomes after they are endocytosed and thereby enter the class II MHC pathway.

I peptidi estranei si trovano negli endosomi

Catena invariante dirige l'MHC verso l'endosoma

ATTIVAZIONE DELLE CELLULE T DA PARTE DELLE CELLULE DENDRITICHE

Interazione del TCR e del CD3 con MHC CD4 (helper) e CD8 (citotossico) si assemblano



LINFOCITI T REGOLATORI (LINFOCITI T SUPPRESSOR)

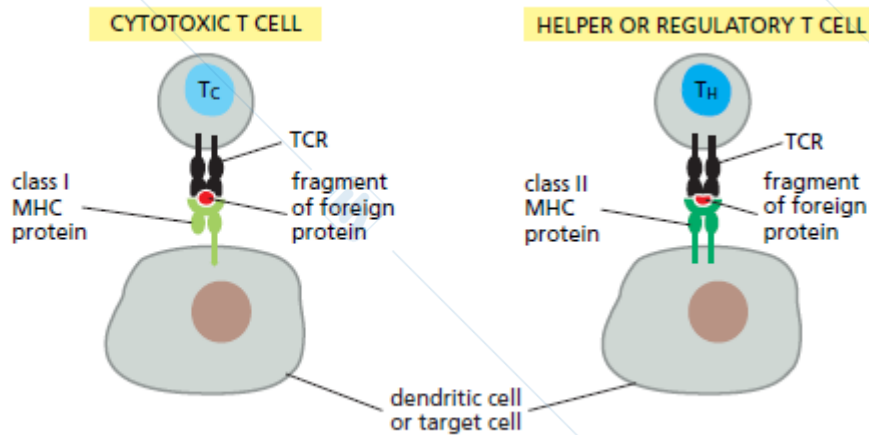
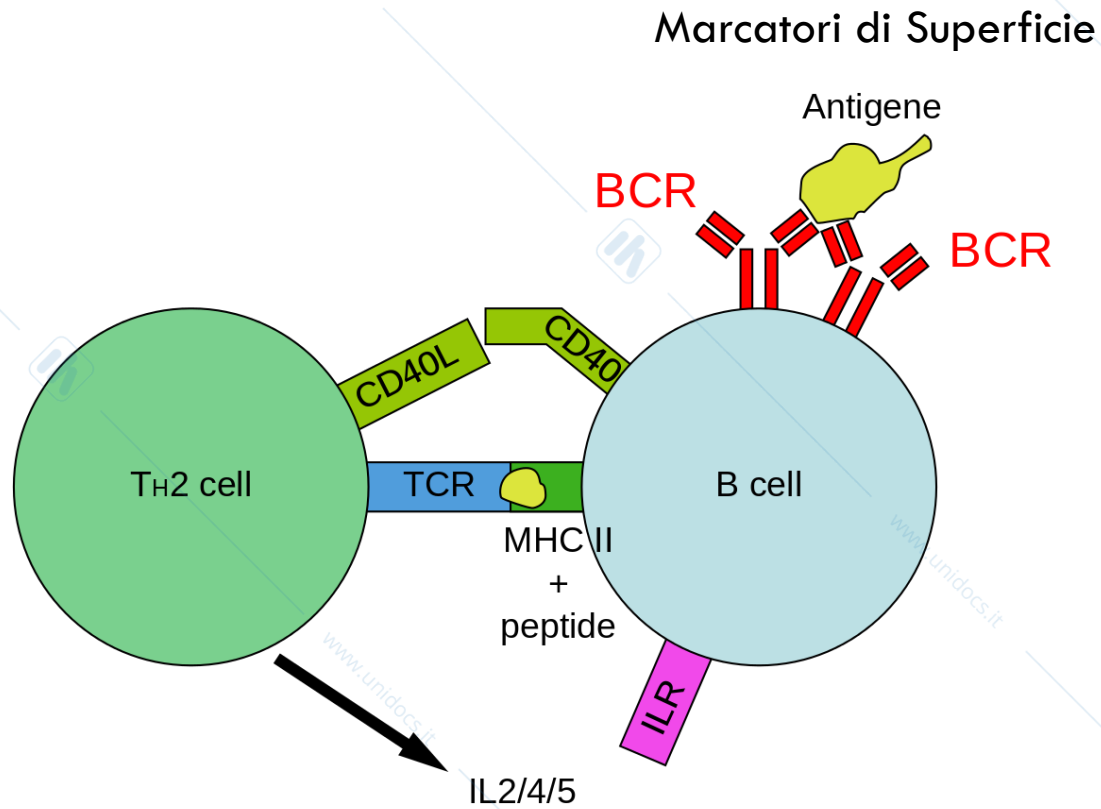
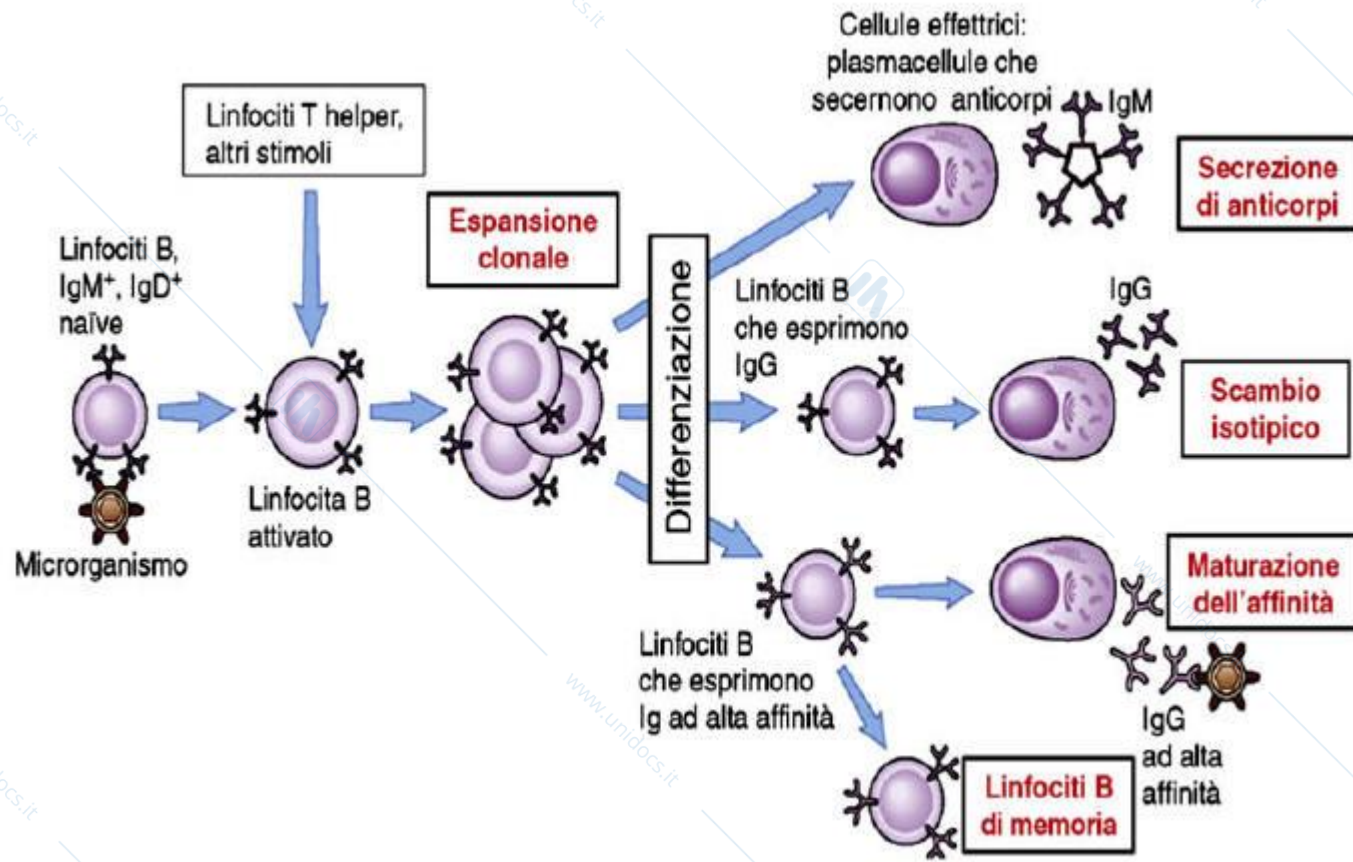


Figure 25–49 Recognition by T cells of foreign peptides bound to MHC proteins. Cytotoxic T cells recognize foreign peptides in association with class I MHC proteins, whereas helper T cells and regulatory T cells recognize foreign peptides in association with class II MHC proteins. In both cases, the T cell recognizes the peptide–MHC complexes on the surface of a dendritic cell or a target cell.

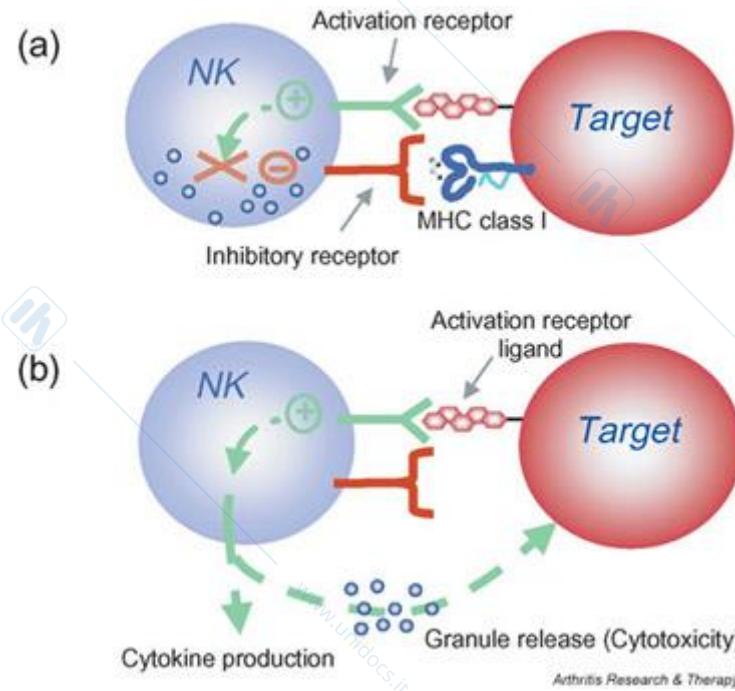
LINFOCITI B



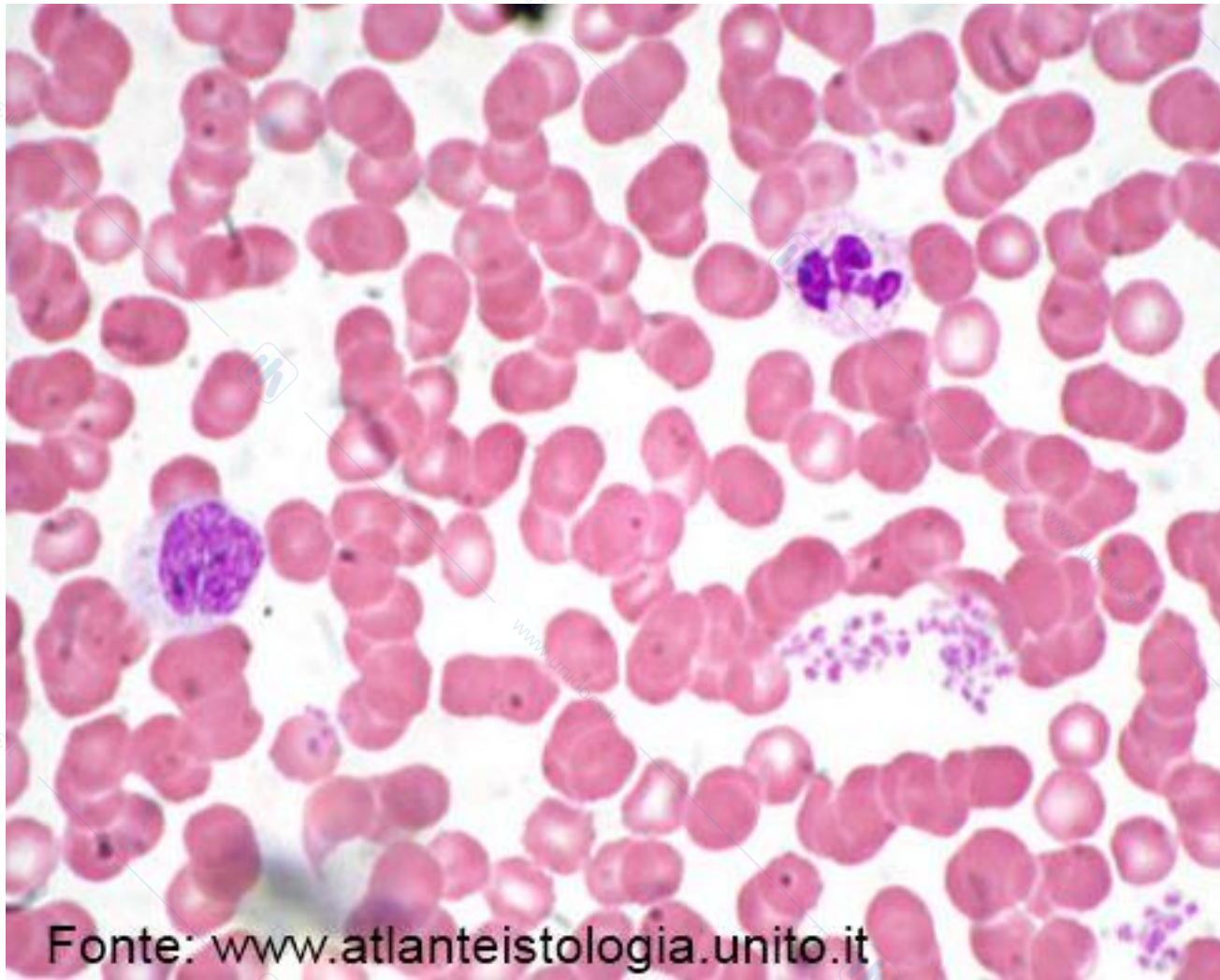
LINFOCITI B



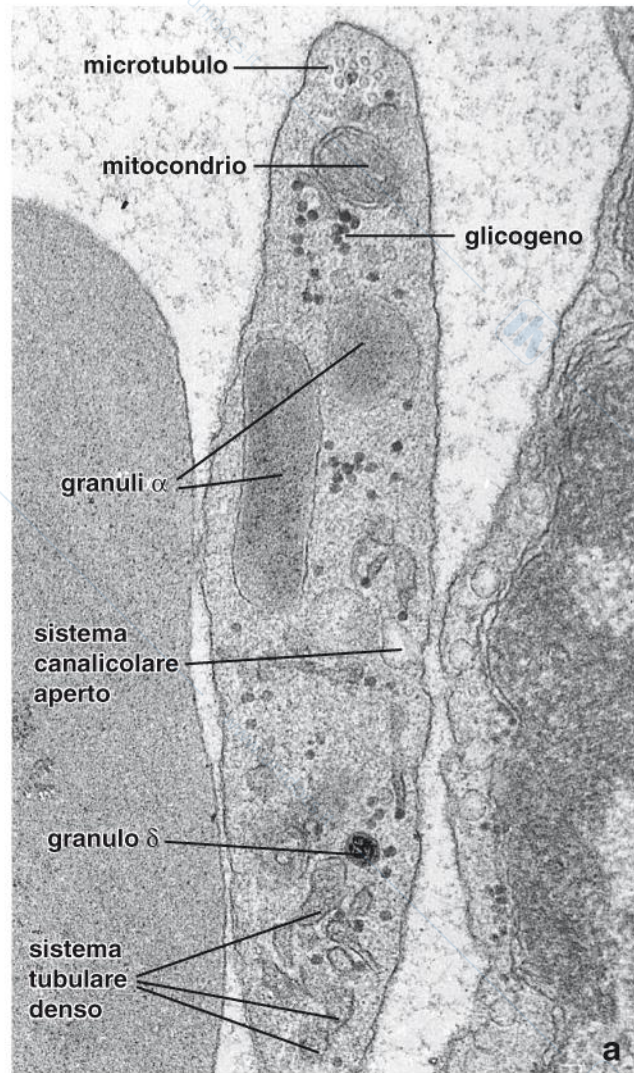
CELLULE NK



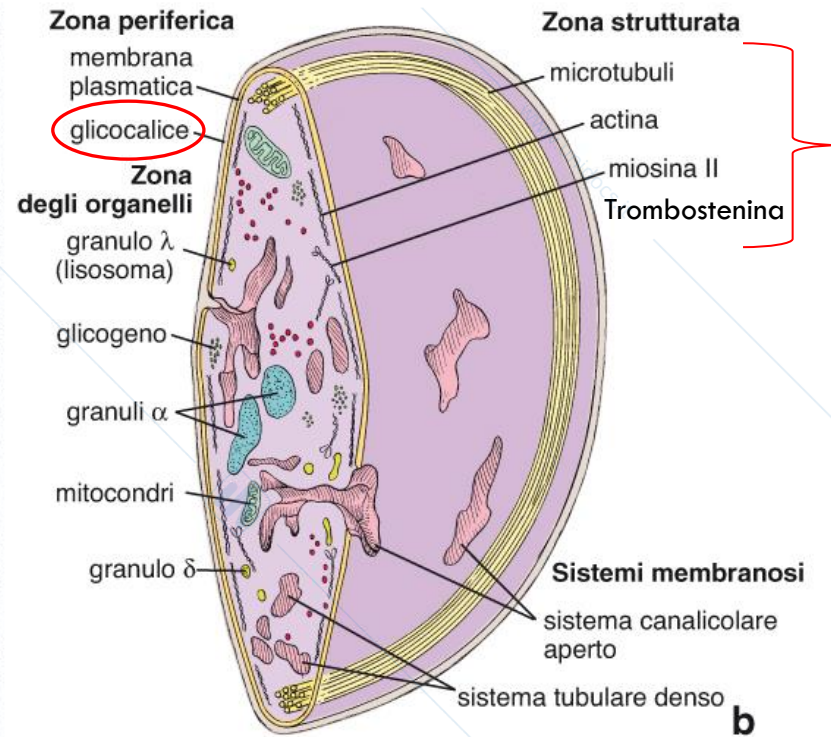
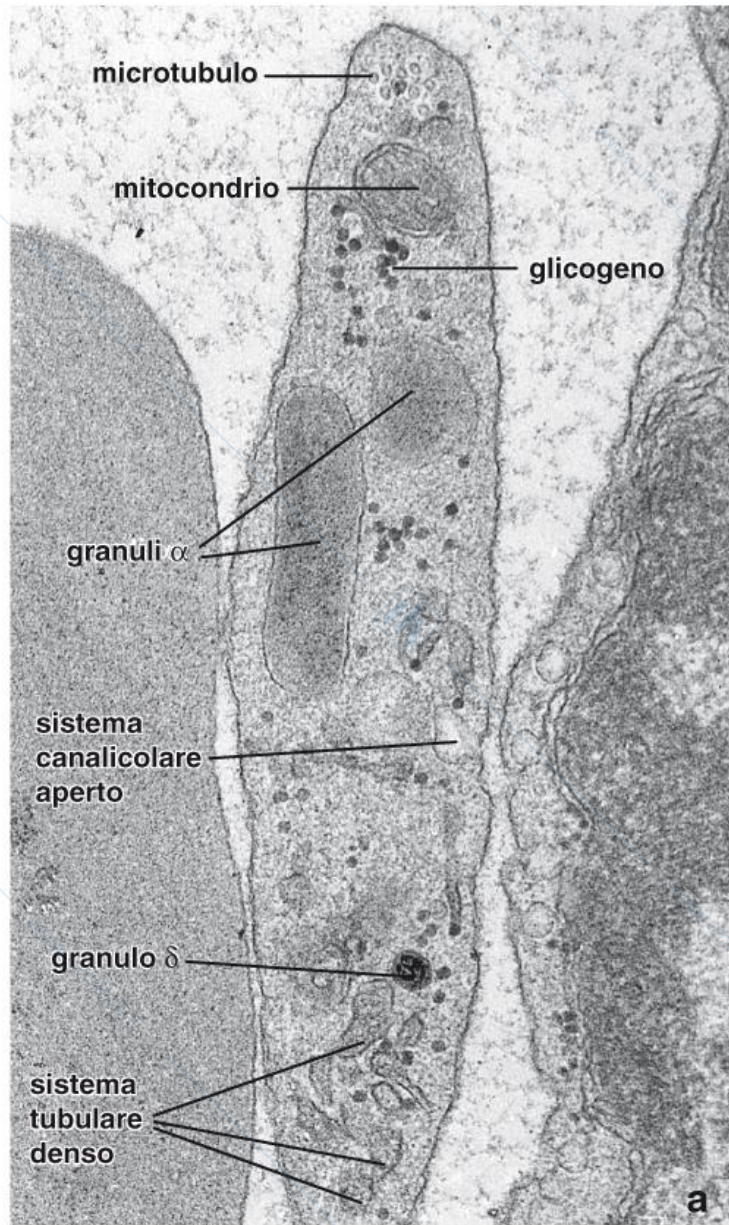
PIASTRINE (TROMBOCITI)



PIASTRINE

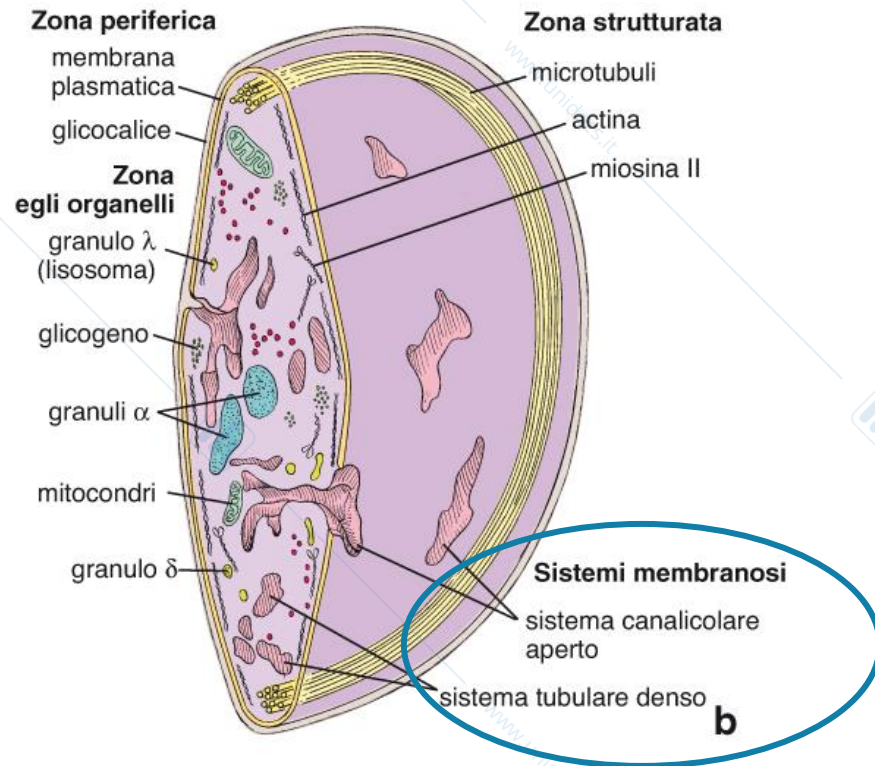


M.H. Ross, W. Pawlina **Istologia, Testo e atlas**

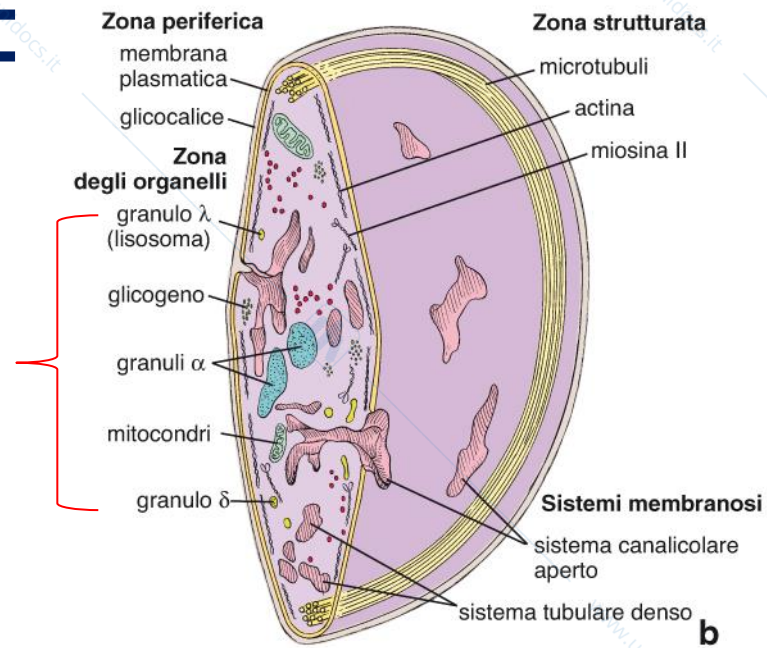


GP1b, GP2B-GP3a
Integrina $\alpha 2\beta 1$

PIASTRINE



PIASTRINE



ante Copyright 2010 C.E.A. Casa Editrice Ambrosiana

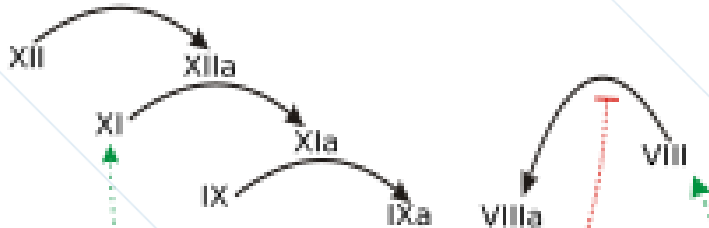
Cascata della coagulazione

Fattori provenienti dal sangue o dalle piastrine

Via intrinseca

(contatto con superficie non endoteliale)

superficie danneggiata

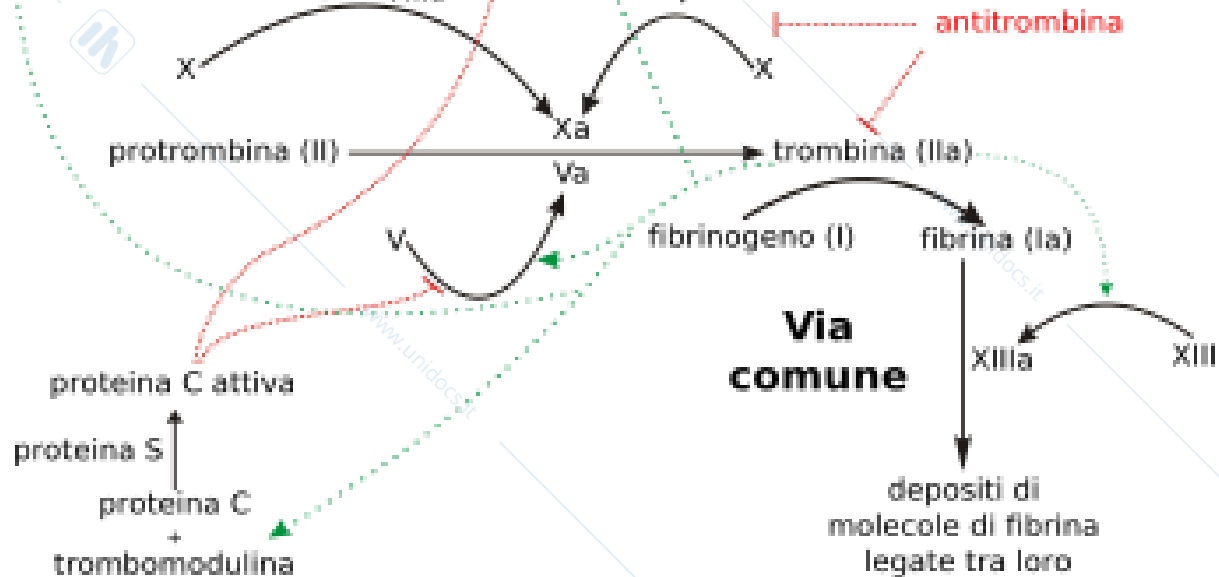
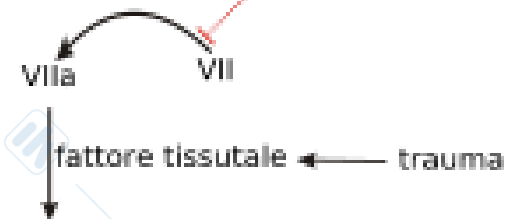


Intervento della tromboplastina tissutale

Via estrinseca

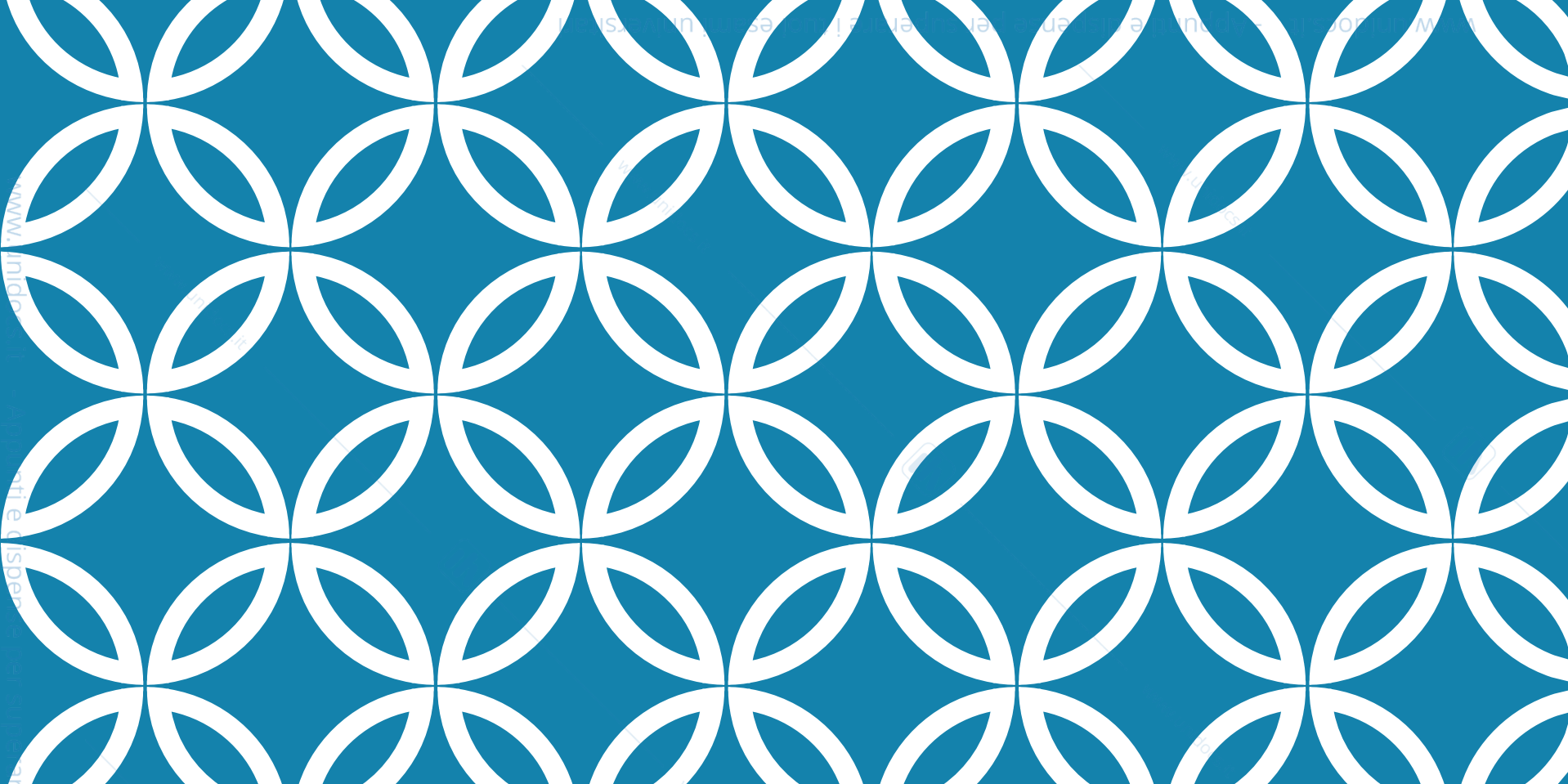
(trauma a livello tissutale)

trauma



Via comune

depositi di molecole di fibrina legate tra loro



EMOPOIESI E MIDOLLO OSSEO

EMOPOIESI

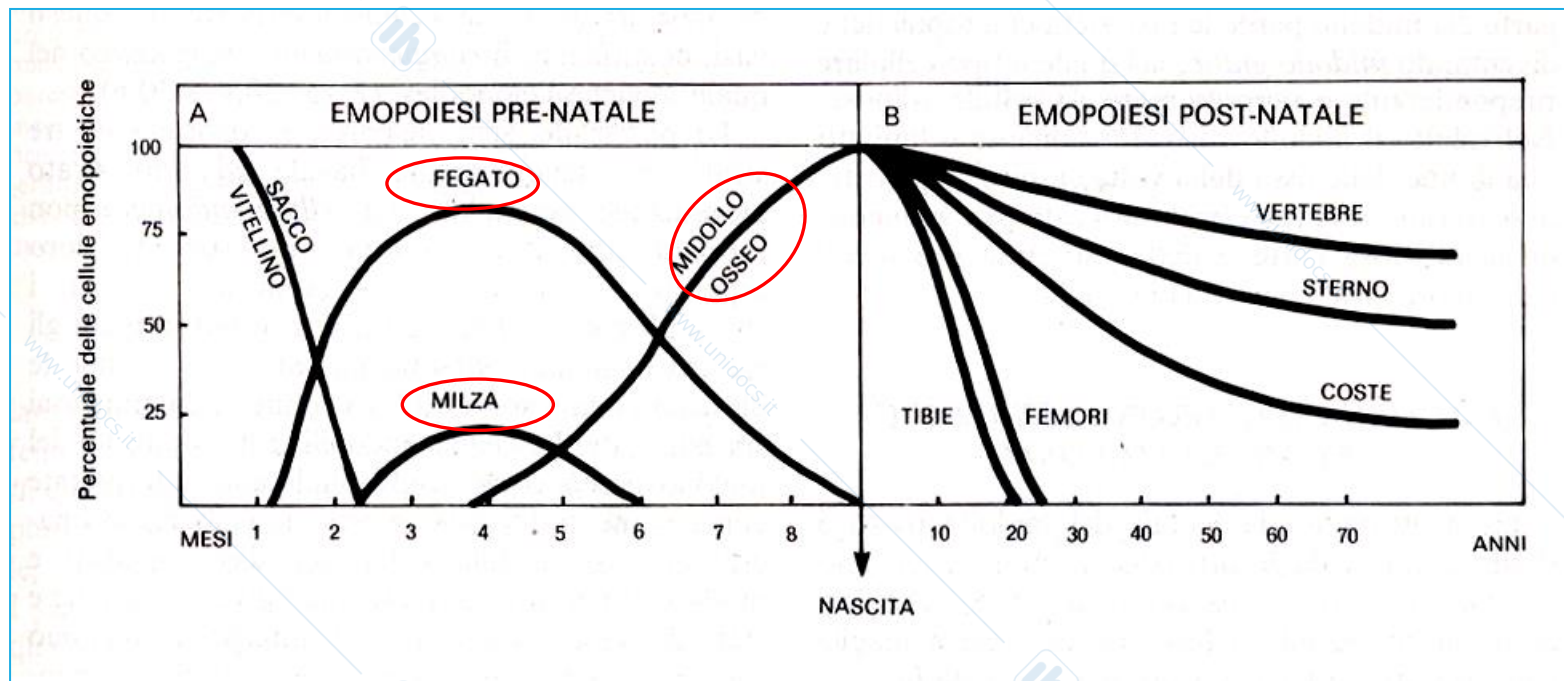
Produzione delle cellule mature presenti nel sangue a partire da cellule staminali emopoietiche

Compartimento delle Cellule staminali
Compartimento dei Progenitori
Compartimento dei Precursori



Emopoiesi

EMOPOIESI- ONTOGENESI



Cellula staminale

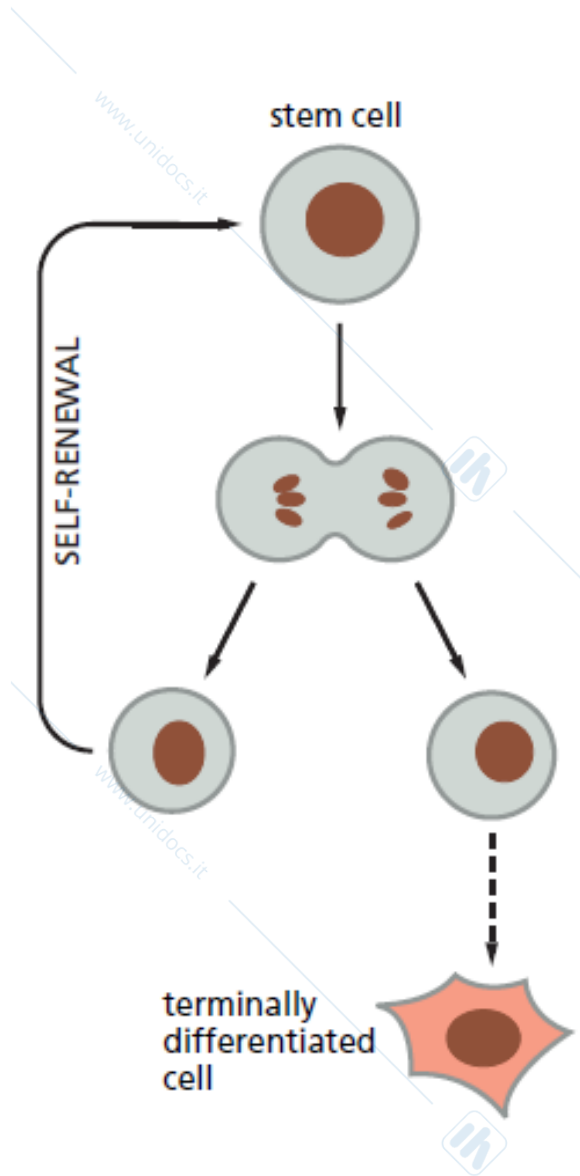


Figure 23-5 The definition of a stem cell. Each daughter produced when a stem cell divides can either remain a stem cell or go on to become terminally differentiated. In many cases, the daughter that opts for terminal differentiation undergoes additional cell divisions before terminal differentiation is completed.

Cellula staminale

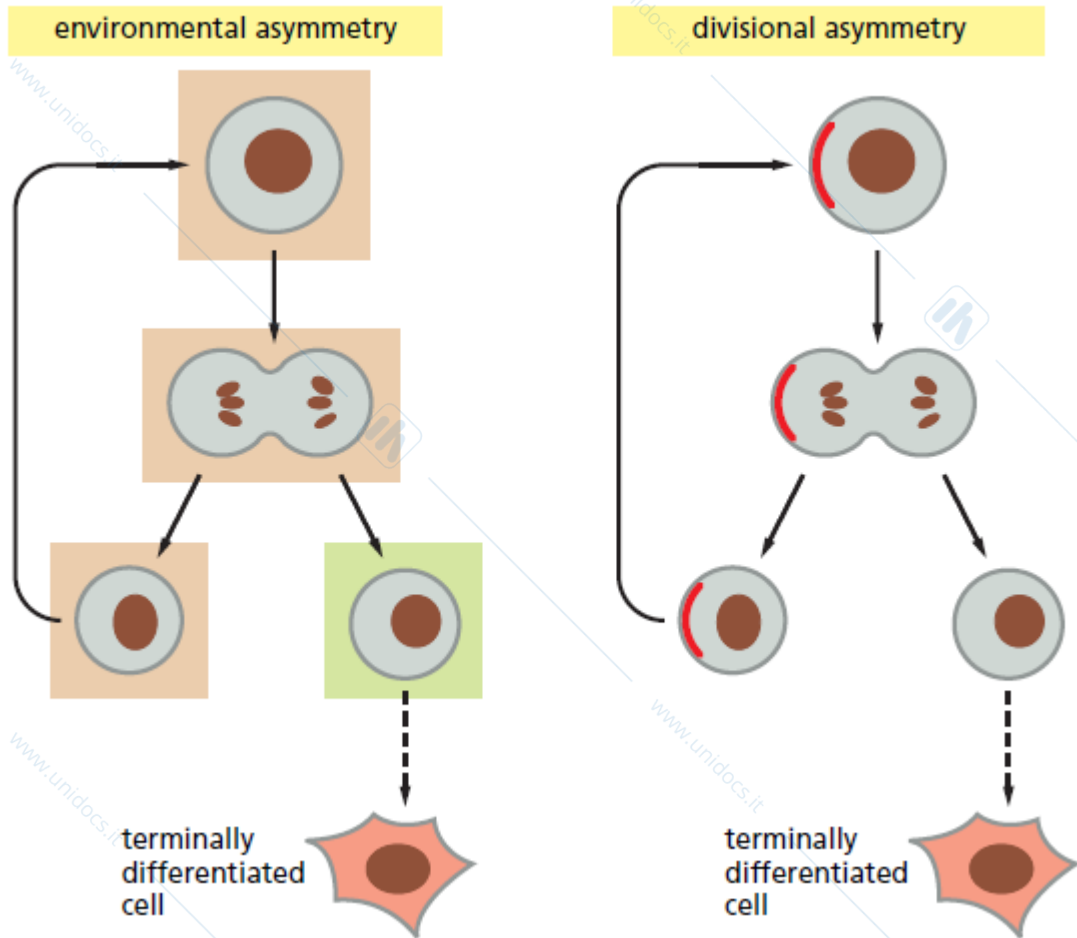


Figure 23–6 Two ways for a stem cell to produce daughters with different fates. In the strategy based on environmental asymmetry, the daughters of the stem cell are initially similar and are directed into different pathways according to the environmental influences that act on them after they are born. The environment is shown as *colored shading* around the cell. With this strategy, the number of stem cells can be increased or reduced to fit the niche available for them. In the strategy based on divisional asymmetry, the stem cell has an internal asymmetry and divides in such a way that its two daughters are already endowed with different determinants at the time of their birth. In some cases, the choice between the alternative fates may be made at random for each daughter, but with a defined probability, like a coin-toss, reflecting the intrinsic randomness or “noise” in all genetic control systems (discussed in Chapter 7).

Midollo Osseo

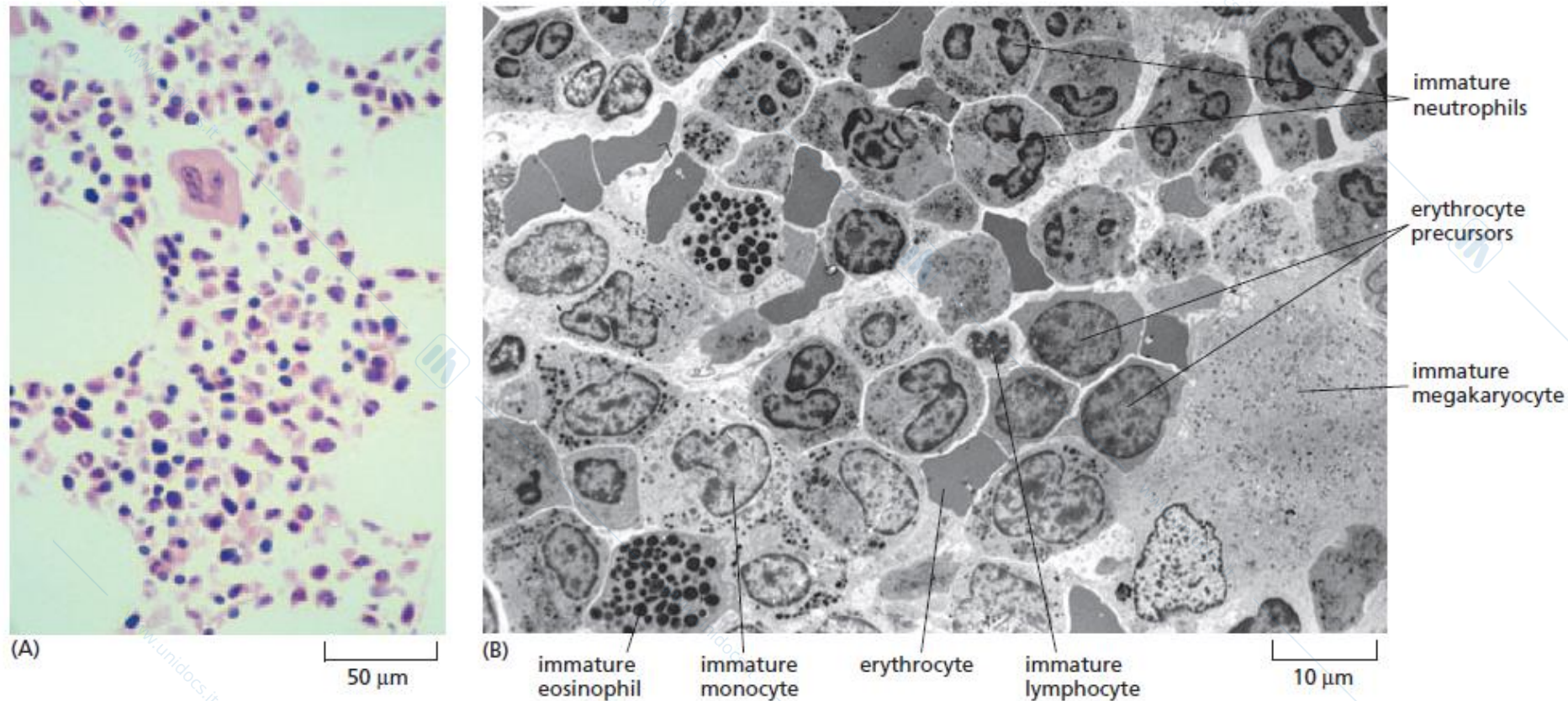
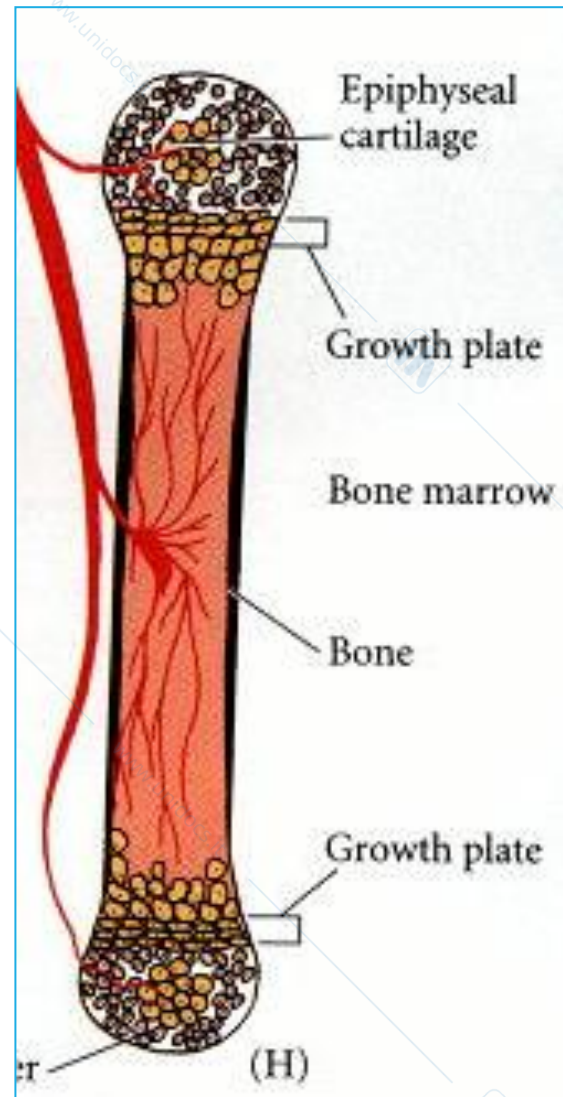


Figure 23-39 Bone marrow. (A) A light micrograph of a stained section. The large empty spaces correspond to fat cells, whose fatty contents have been dissolved away during specimen preparation. The giant cell with a lobed nucleus is a megakaryocyte. (B) A low-magnification electron micrograph. Bone marrow is the main source of new blood cells (except for T lymphocytes, which are produced in the thymus). Note that the immature blood cells of a particular type tend to cluster in "family groups." (A, courtesy of David Mason; B, from J.A.G. Rhodin, *Histology: A Text and Atlas*. New York: Oxford University Press, 1974.)

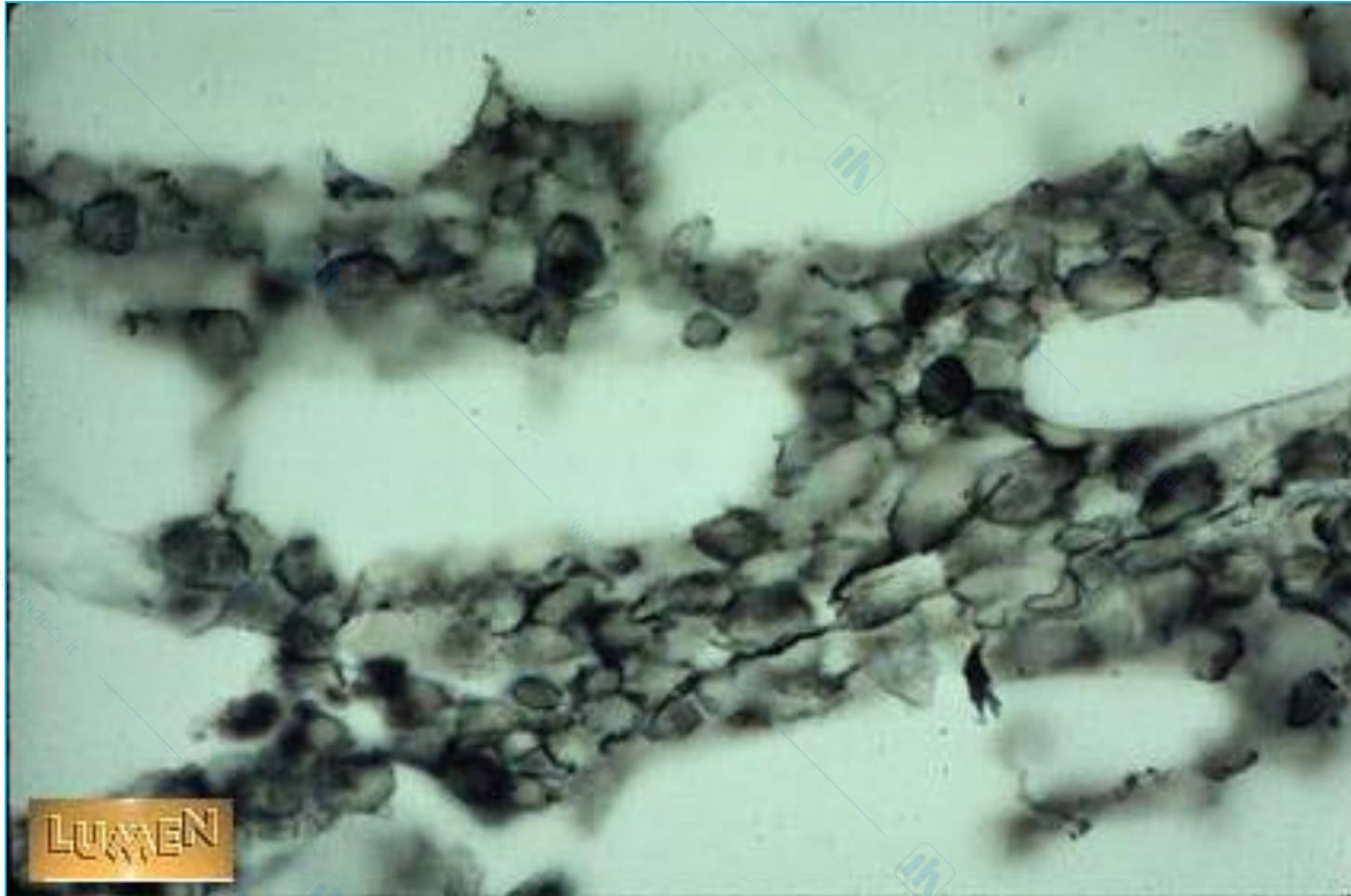
Compartimento Vascolare

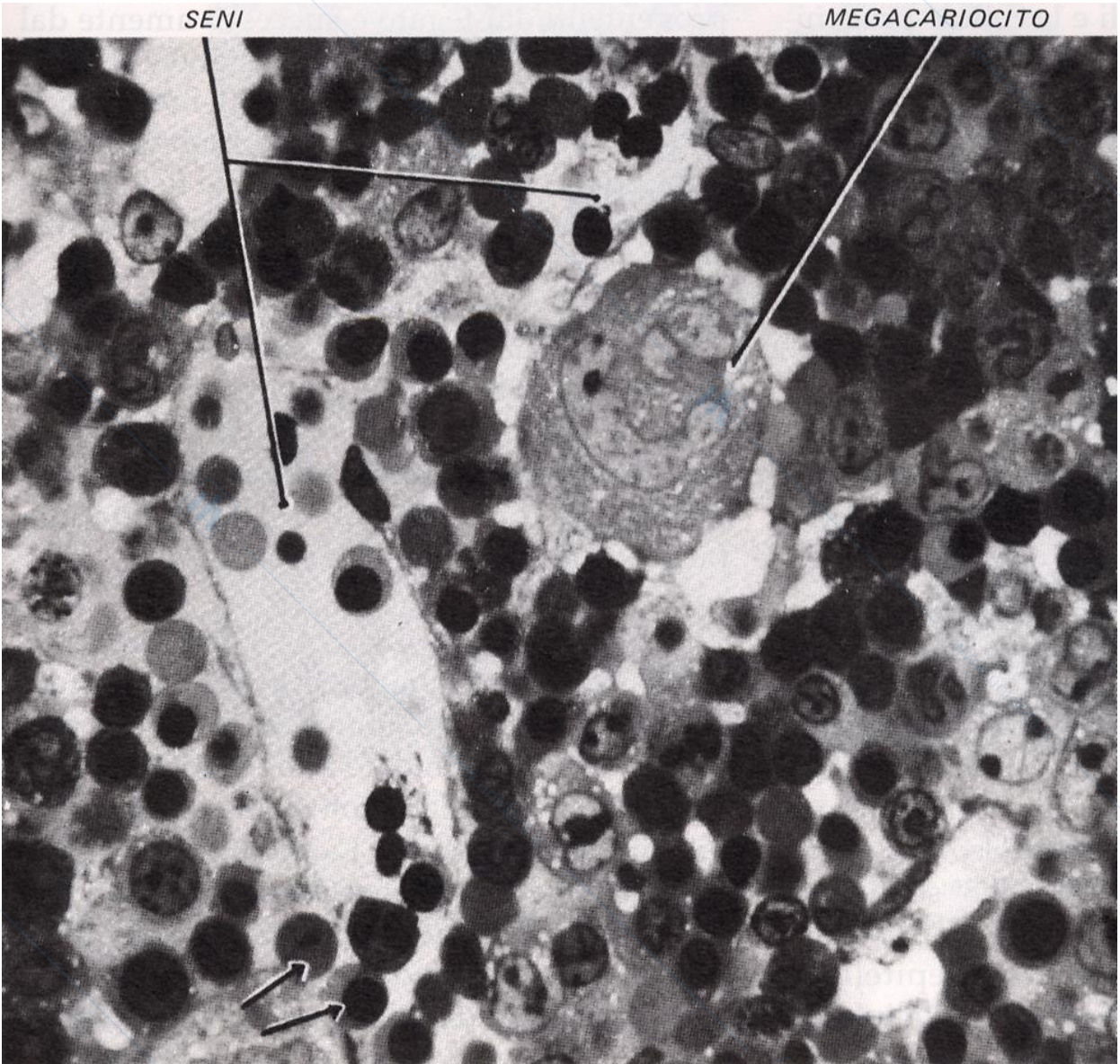


Seni Venosi



Stroma Reticolare



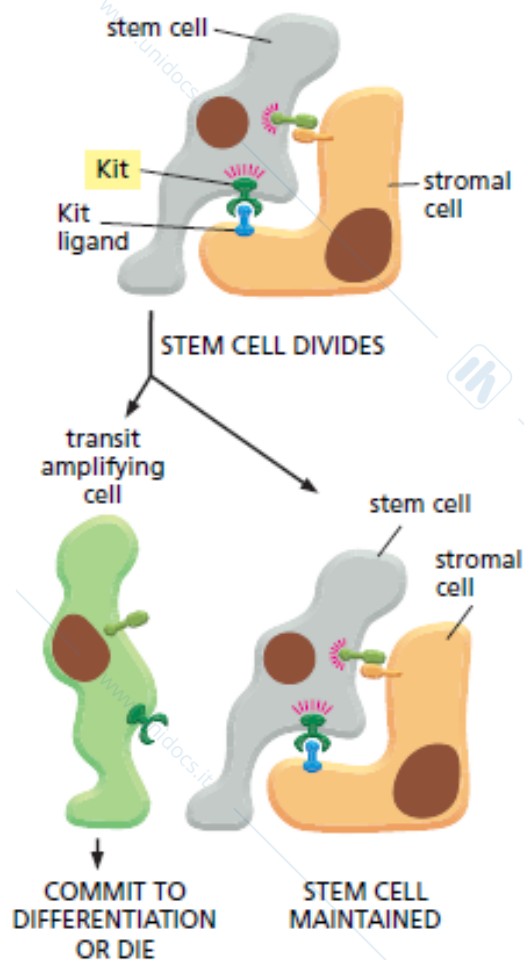


ALTRE FUNZIONI DEL MIDOLLO OSSEO

- Attività emoclasica o emocateretica
- Attività fagocitaria mediata dai macrofagi
- Funzioni osteogeniche
- Funzioni immunologiche

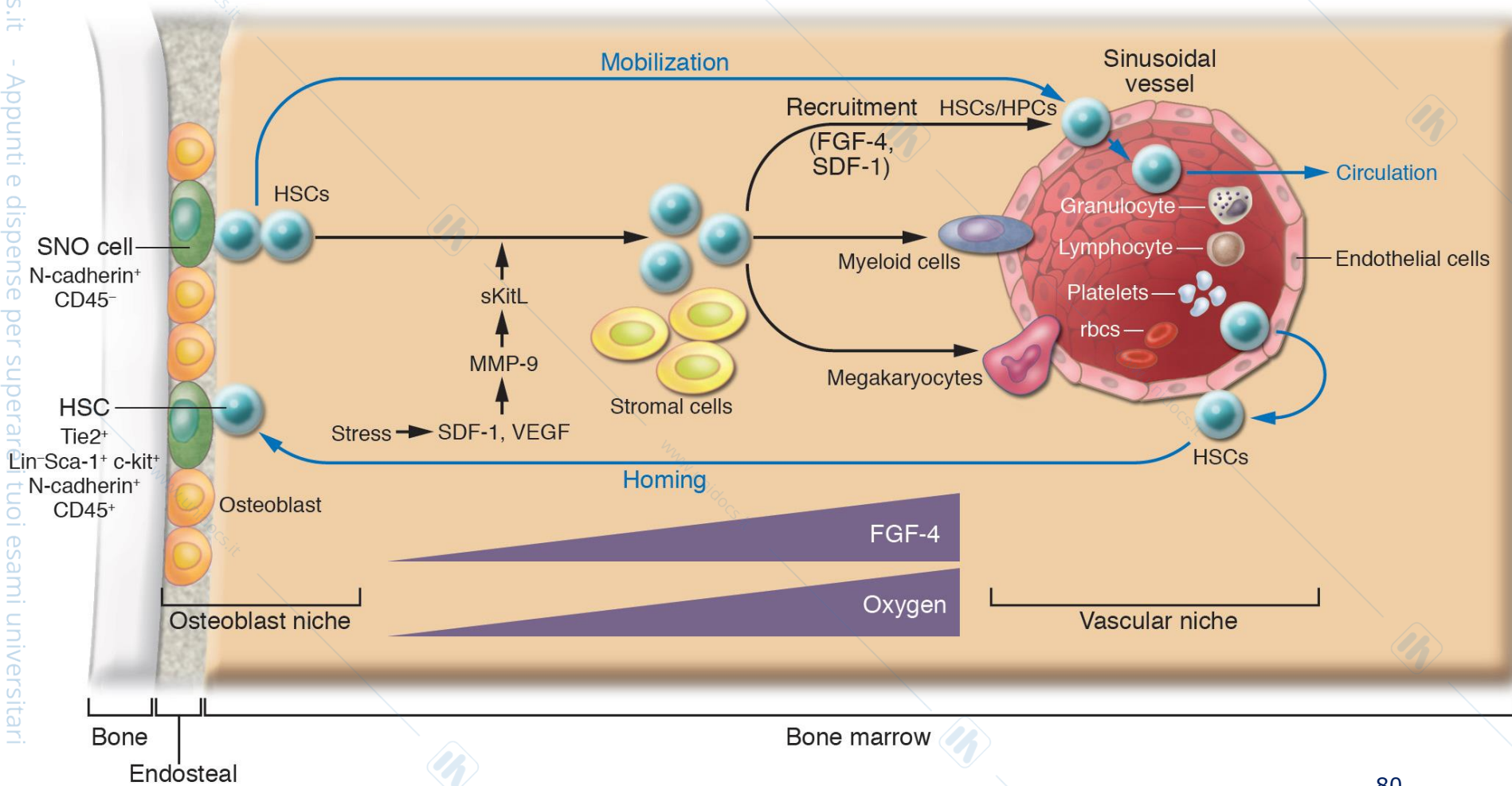
Cellule Staminali Emopoietiche (CSE)

Dipendenza delle cellule staminali emopoietiche dal contatto con le cellule stromali ("supporting cells")



Nicchia

Nicchia osteoblastica Nicchia vascolare



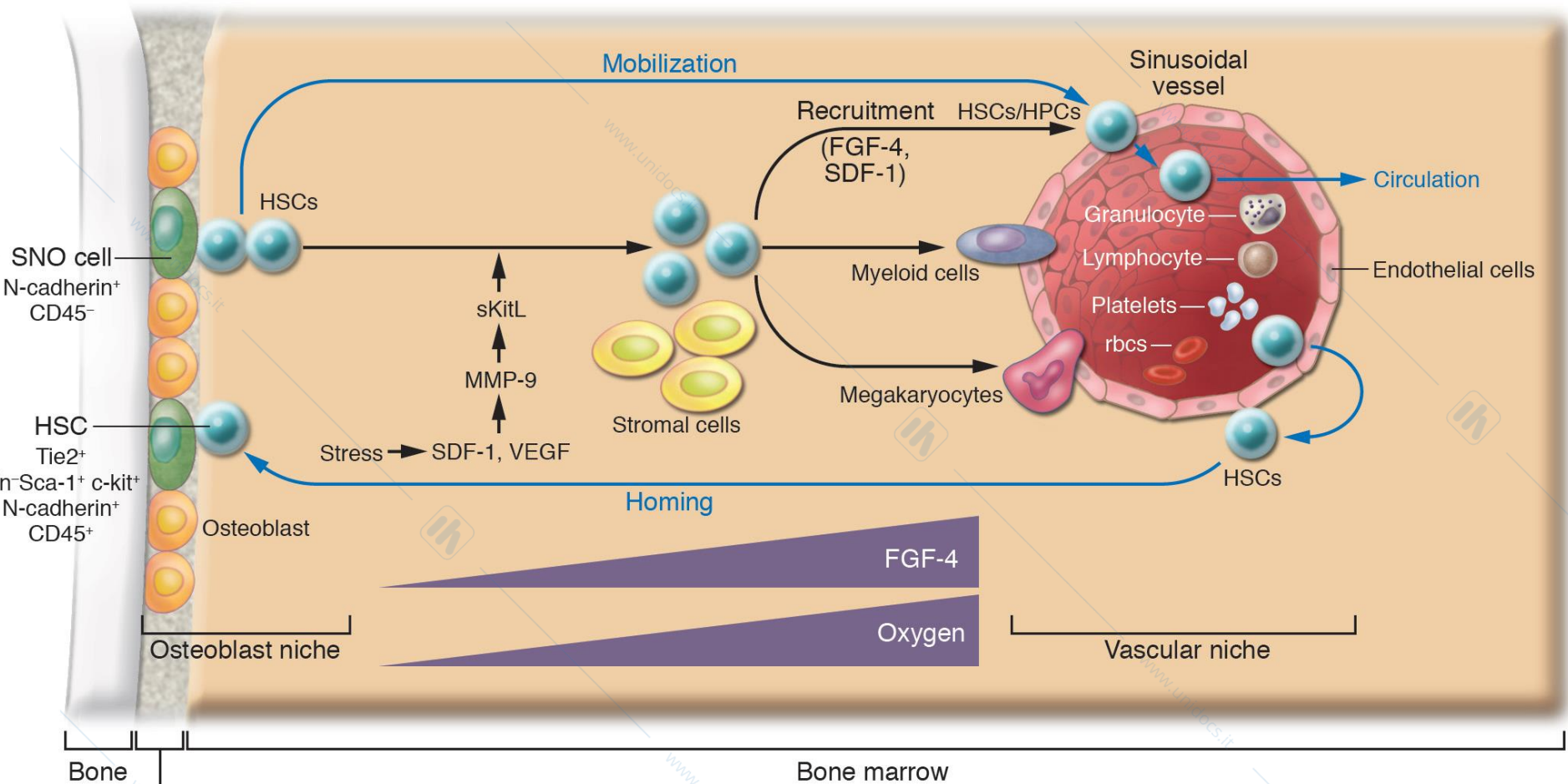


Figure 2 Endosteal

The osteoblastic and vascular niches in bone. Under normal physiological conditions, HSCs reside in either the osteoblastic or vascular niche. A portion of HSC daughter cells, in response to changes in levels of SDF-1 in the BM, will leave the niche and begin to mobilize and circulate. HSC mobilization is the reverse of homing, occurring in response to higher levels of SDF-1 in the BM. The osteoblastic niche may provide a quiescent microenvironment for HSC maintenance. In contrast, the vascular niche facilitates HSC transendothelial migration during mobilization or homing and may favor HSC proliferation and further differentiation. The process of recruiting HPCs to the vascular niche may depend on endothelium-derived FGF-4 and SDF-1. Higher FGF-4 and oxygen concentration gradients as the cells progress from the osteoblastic niche to the vascular niche might play a role in recruitment, proliferation, and differentiation of HSCs/HPCs. Under stress such as thrombocytopenia, SDF-1 and VEGF activate MMP-9, which converts membrane-associated Kit ligand into soluble Kit ligand (sKitL) and in turn promotes HSCs entry into the cell cycle, mobilization to the vascular niche, and differentiation (34).

Regolazione dell'emopoiesi

Table 23–2 Some Colony-stimulating Factors (CSFs) That Influence Blood Cell Formation

FACTOR	TARGET CELLS	PRODUCING CELLS	RECEPTORS
Erythropoietin	CFC-E	kidney cells	cytokine family
Interleukin 3 (IL3)	multipotent stem cell, most progenitor cells, many terminally differentiated cells	T lymphocytes, epidermal cells	cytokine family
Granulocyte/macrophage CSF (GMCSF)	GM progenitor cells	T lymphocytes, endothelial cells, fibroblasts	cytokine family
Granulocyte CSF (GCSF)	GM progenitor cells and neutrophils	macrophages, fibroblasts	cytokine family
Macrophage CSF (MCSF)	GM progenitor cells and macrophages	fibroblasts, macrophages, endothelial cells	receptor tyrosine kinase family
Kit ligand	hemopoietic stem cells	stromal cells in bone marrow and many other cells	receptor tyrosine kinase family

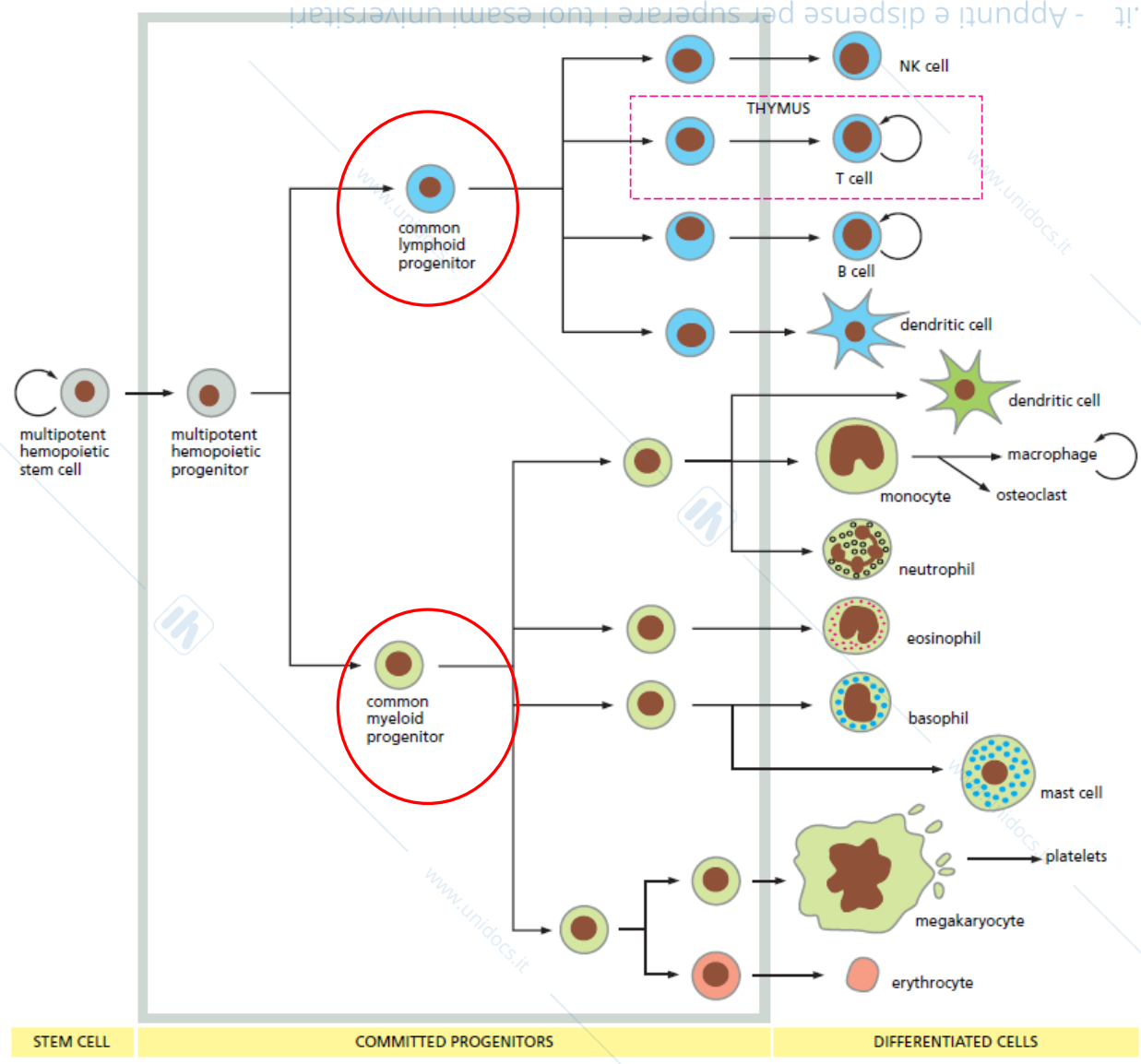


Figure 23-42 A tentative scheme of hemopoiesis. The multipotent stem cell normally divides infrequently to generate either more multipotent stem cells, which are self-renewing, or committed progenitor cells, which are limited in the number of times that they can divide before differentiating to form mature blood cells. As they go through their divisions, the progenitors become progressively more specialized in the range of cell types that they can give rise to, as indicated by the branching of the cell-lineage diagram in the region enclosed in the gray box. Many of the details of this part of the lineage diagram are still controversial, however. In adult mammals, all of the cells shown develop mainly in the bone marrow—except for T lymphocytes, which develop in the thymus, and macrophages and osteoclasts, which develop from blood monocytes. Some dendritic cells may also derive from monocytes.

EMOPOIESI

C.Staminale Linfoide:

Linfociti B e T

C.staminale mieloide:

CFU-GEMM (Unità formanti colonie granulocitarie, eritroidi, mielomonocitarie e megacariocitarie)

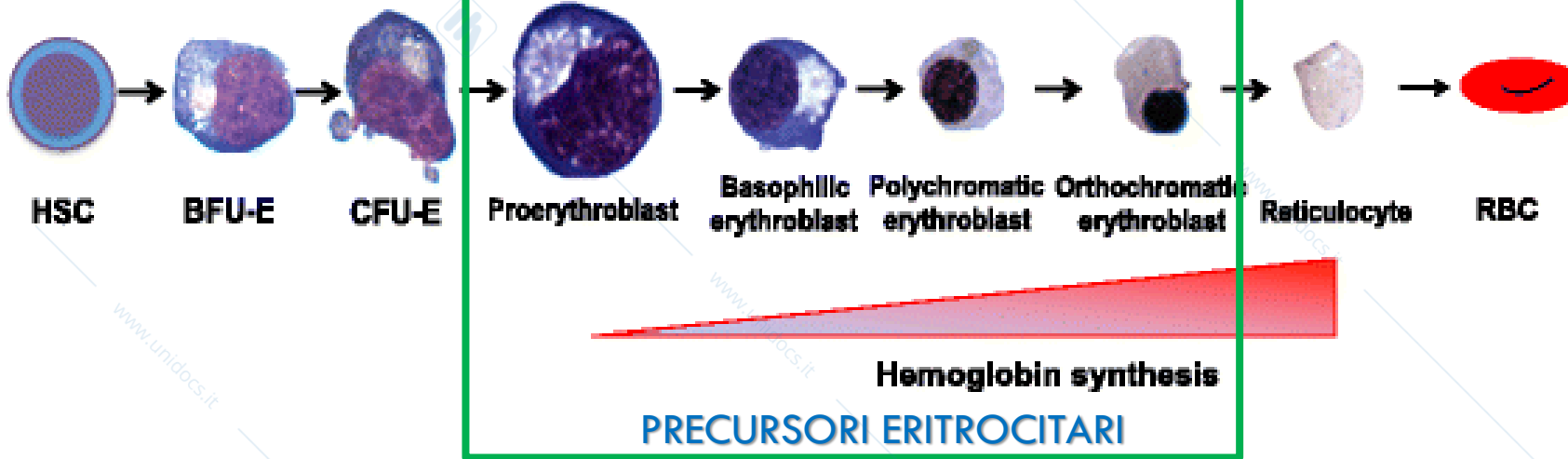
ERITROPOIESI

IL-3, GM-CSF, SCF (c-kit ligand)

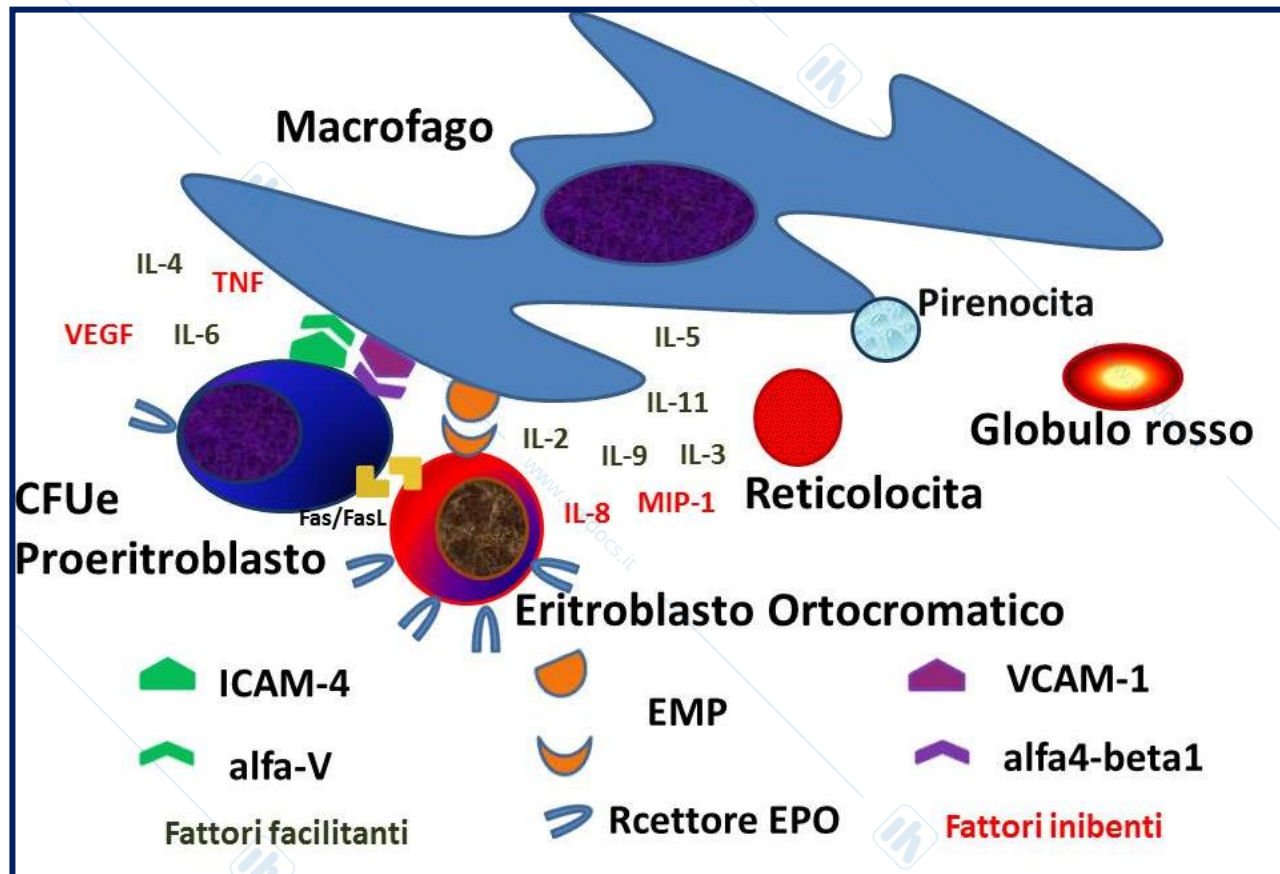
ERITROPOIETINA

Erythroblastic Islands

Bloodstream

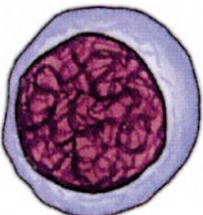


Isolotti eritroblastici



Precursori Eritrocitari

20-25 μm
Citoplasma
basofilo
Mitosi
Hb < 2%



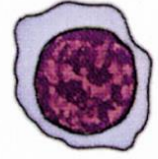
Proeritroblasto



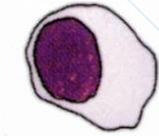
Eritroblasto
basofilo

15 -20 μm
Citoplasma
intensamente
basofilo mitosi
Hb 2-10%

9-12 μm
coesistenza
di basofilia
(ribosomi) e
di acidofilia
(Hb 10-20%)
Scomparsa
del-nucleolo



Eritroblasto
policromatofilo



Eritroblasto
ortocromatofilo

8-10 μm
Acidofilo
nucleo
eccentrico e
picnotico
che viene
espulso
NO mitosi

Presenza di
ribosomi
Col.blu cresile
brillante
0.8% sangue

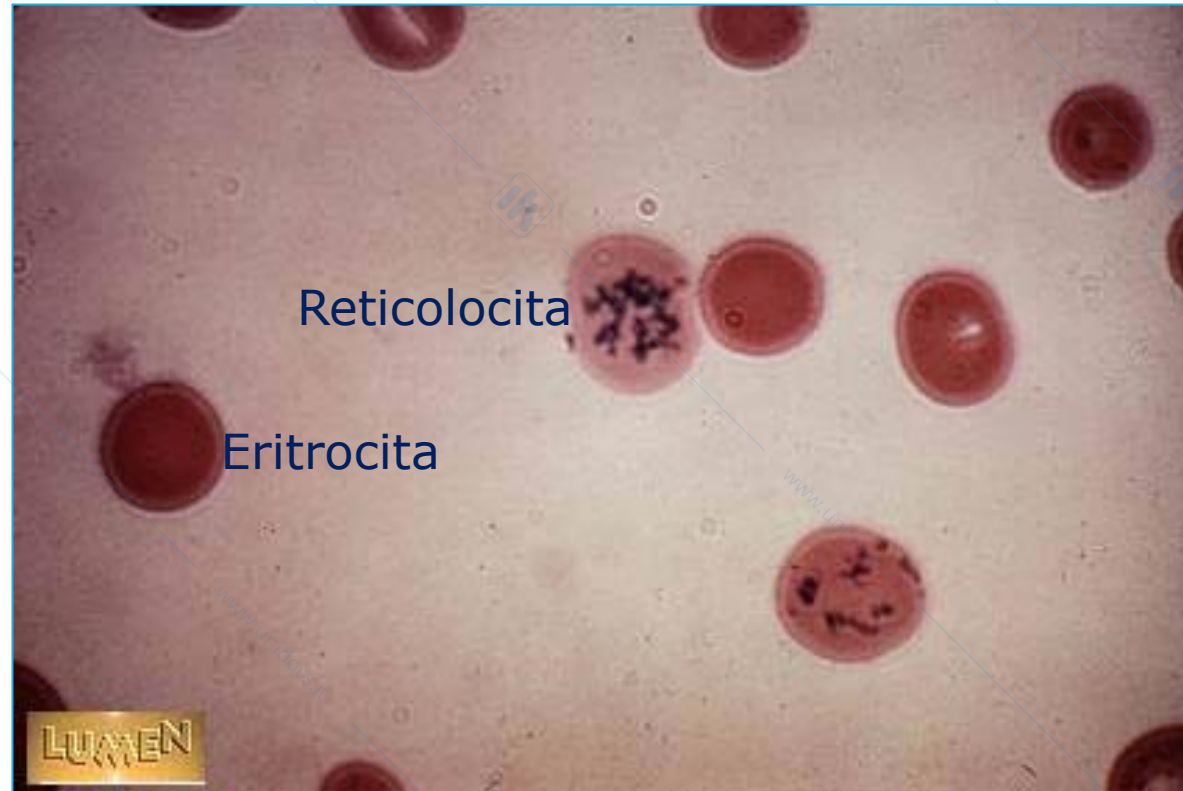
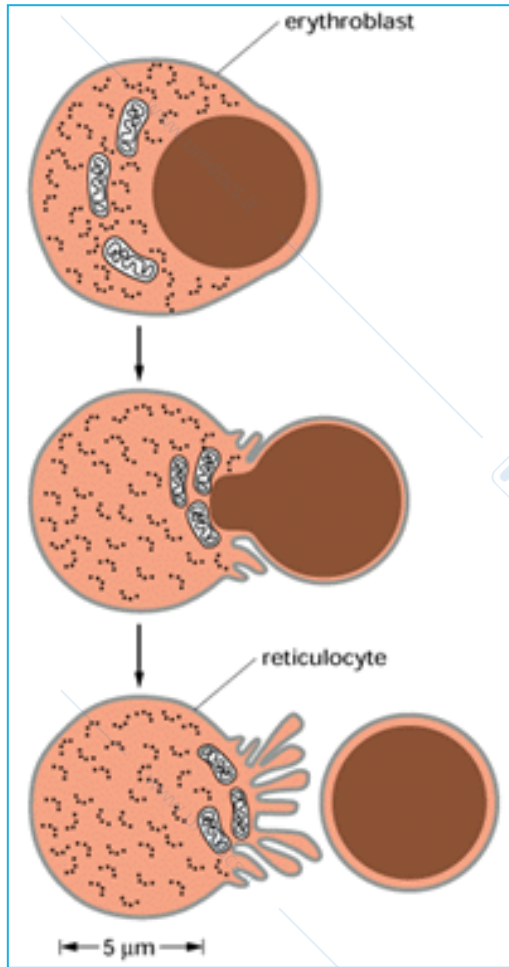


Reticolocita

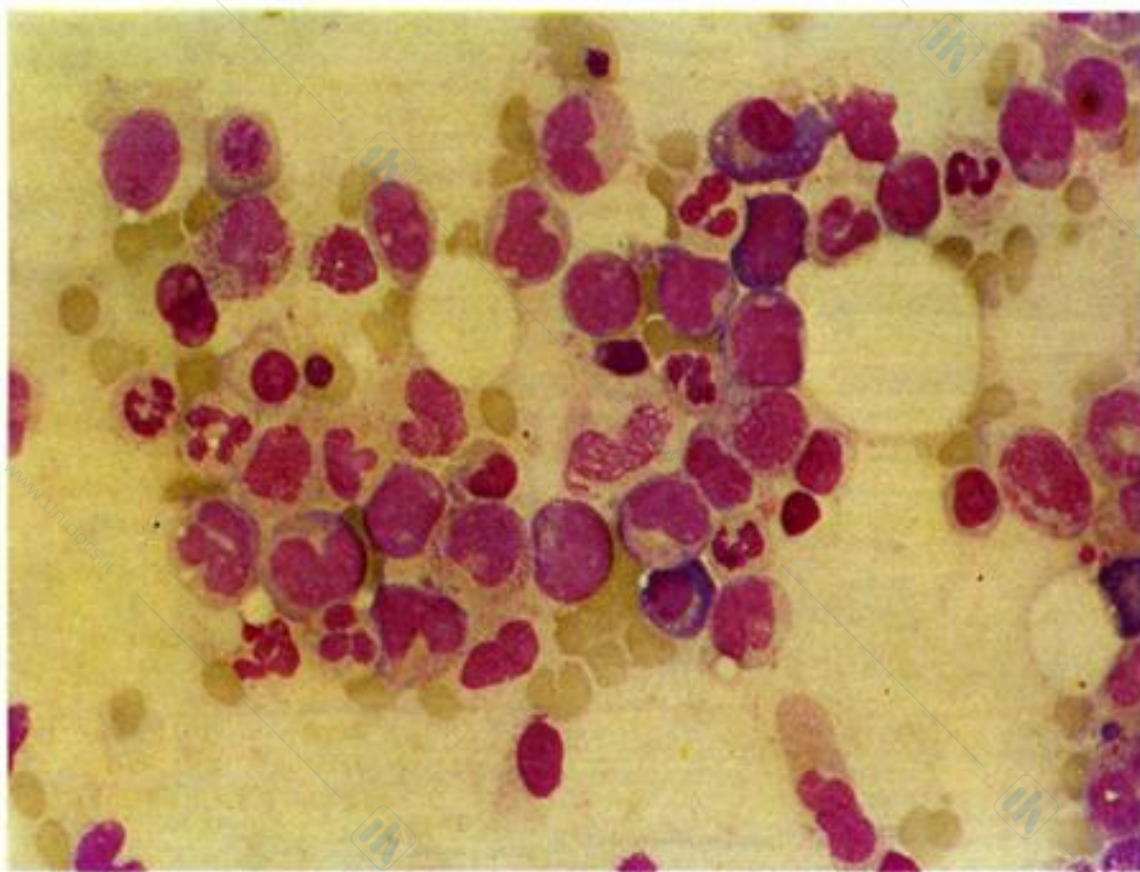


Eritrocita

Eritropoiesi

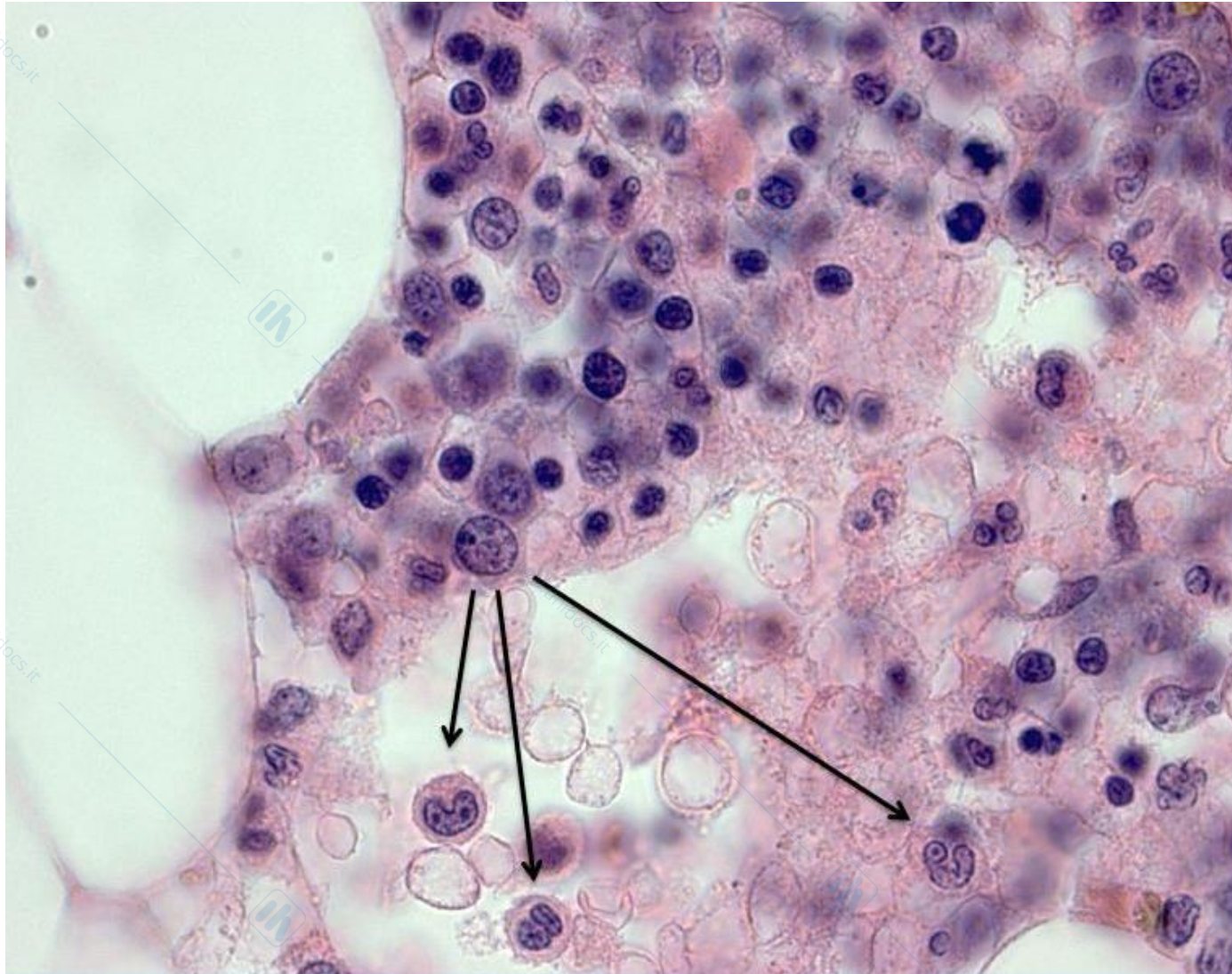


GRANULOCITOPOIESI

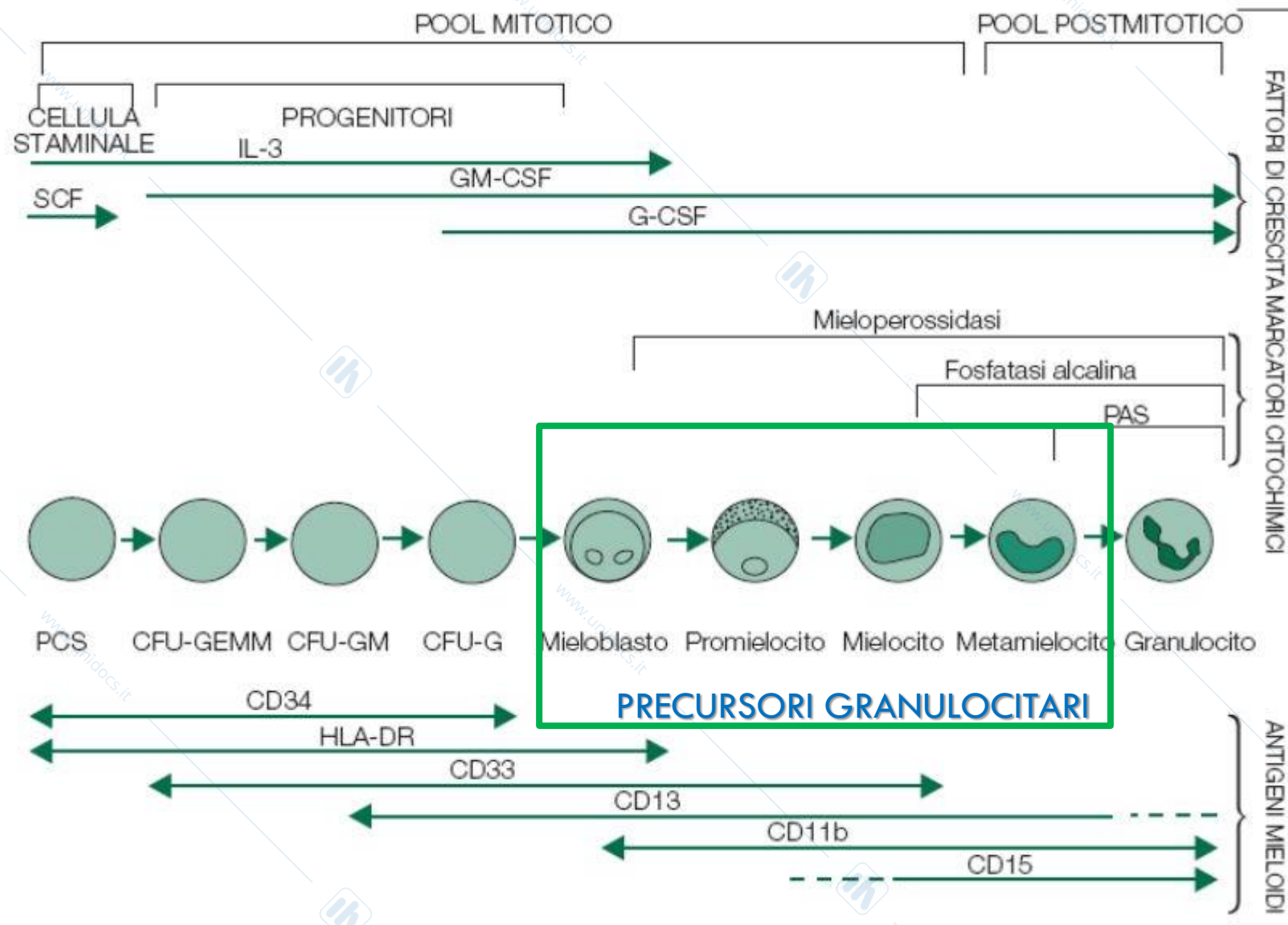


Cellule della serie granulocitaria a vario livello di maturazione.

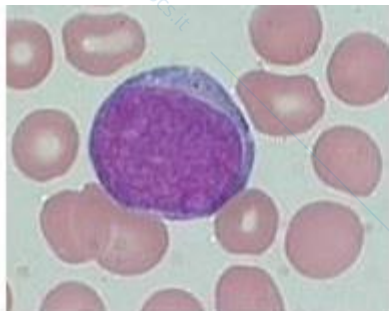
GRANULOCITOPOIESI



Granulocitopoiesi

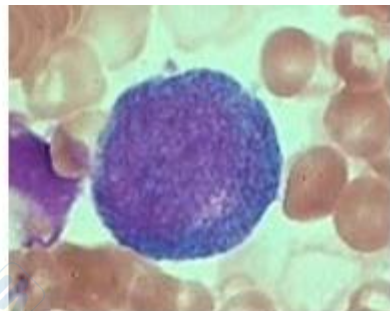


Granulocitopoiesi



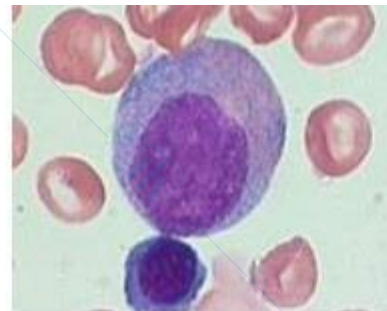
A: mieloblasto

14 μm
Citoplasma
basofilo
privo di
granulazioni



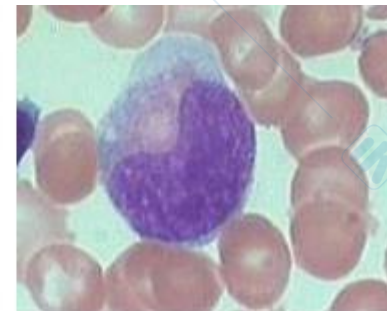
B: promielocita

20 μm
Granuli
azzurrofilo



C: mielocita

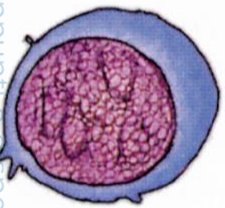
14-18 μm
Citoplasma
Debolmente
acidofilo
comparsa di
granulazioni
specifiche.



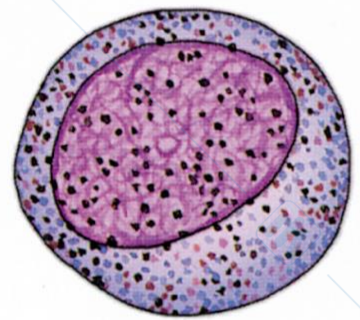
D: metamielocita

NO mitosi
Nucleo a
ferro di
cavallo

Attività mitotica

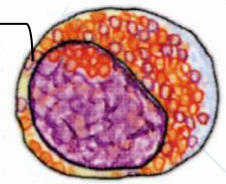


Mieloblasto
12-14 μm

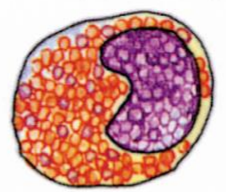


Promielocita
15-20 μm
< basofilia
Granuli azzurr.

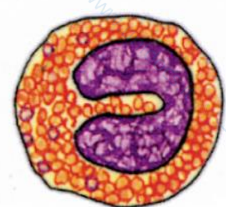
EOSINOFILI



Mielocita eosinofilo



Metamielocita eosinofilo



Cellula eosinofila



Eosinofilo

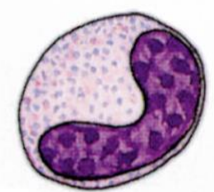
NEUTROFILI



Mielocita neutrofilo



Metamielocita neutrofilo

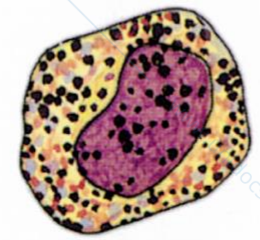


Cellula neutrofila

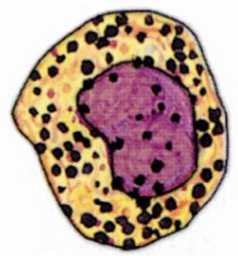


Neutrofilo

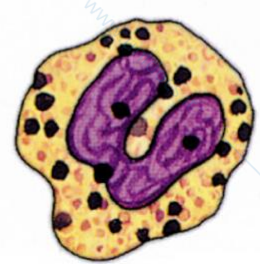
BASOFILI



Mielocita basofilo



Metamielocita basofilo

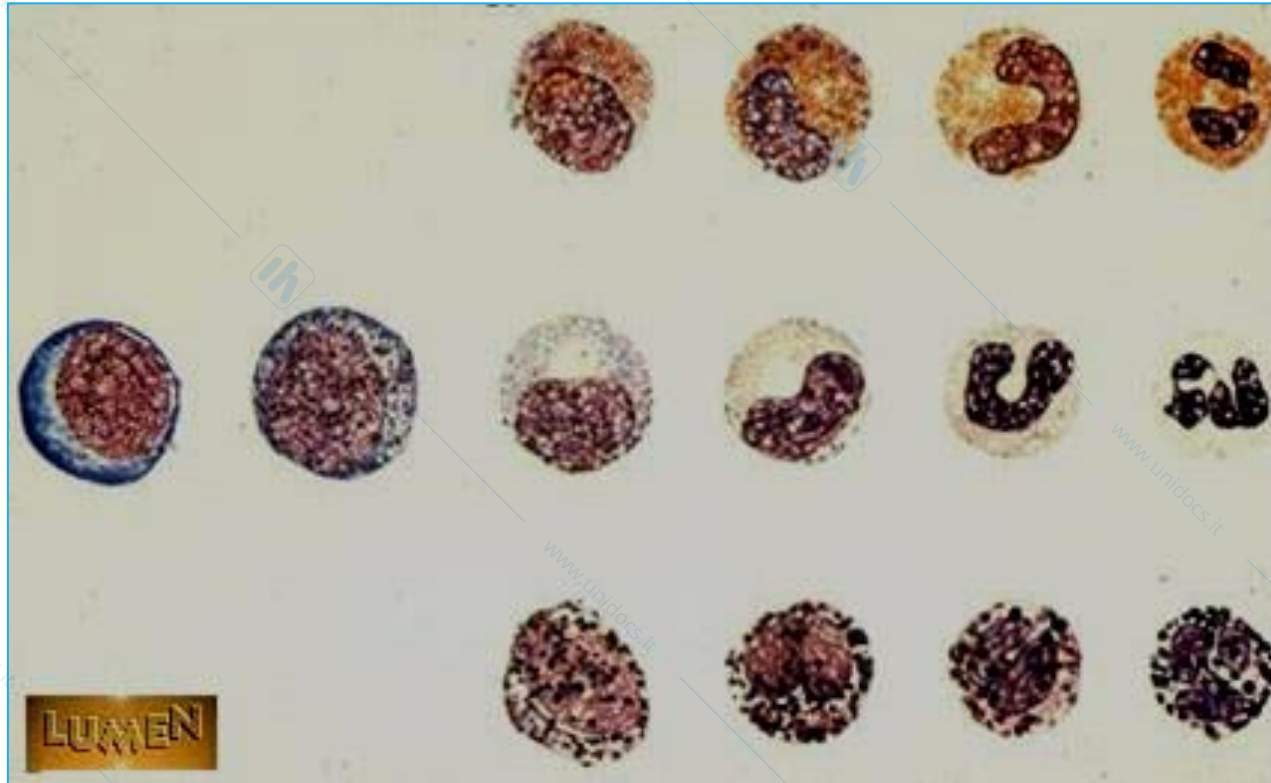


Cellula basofila

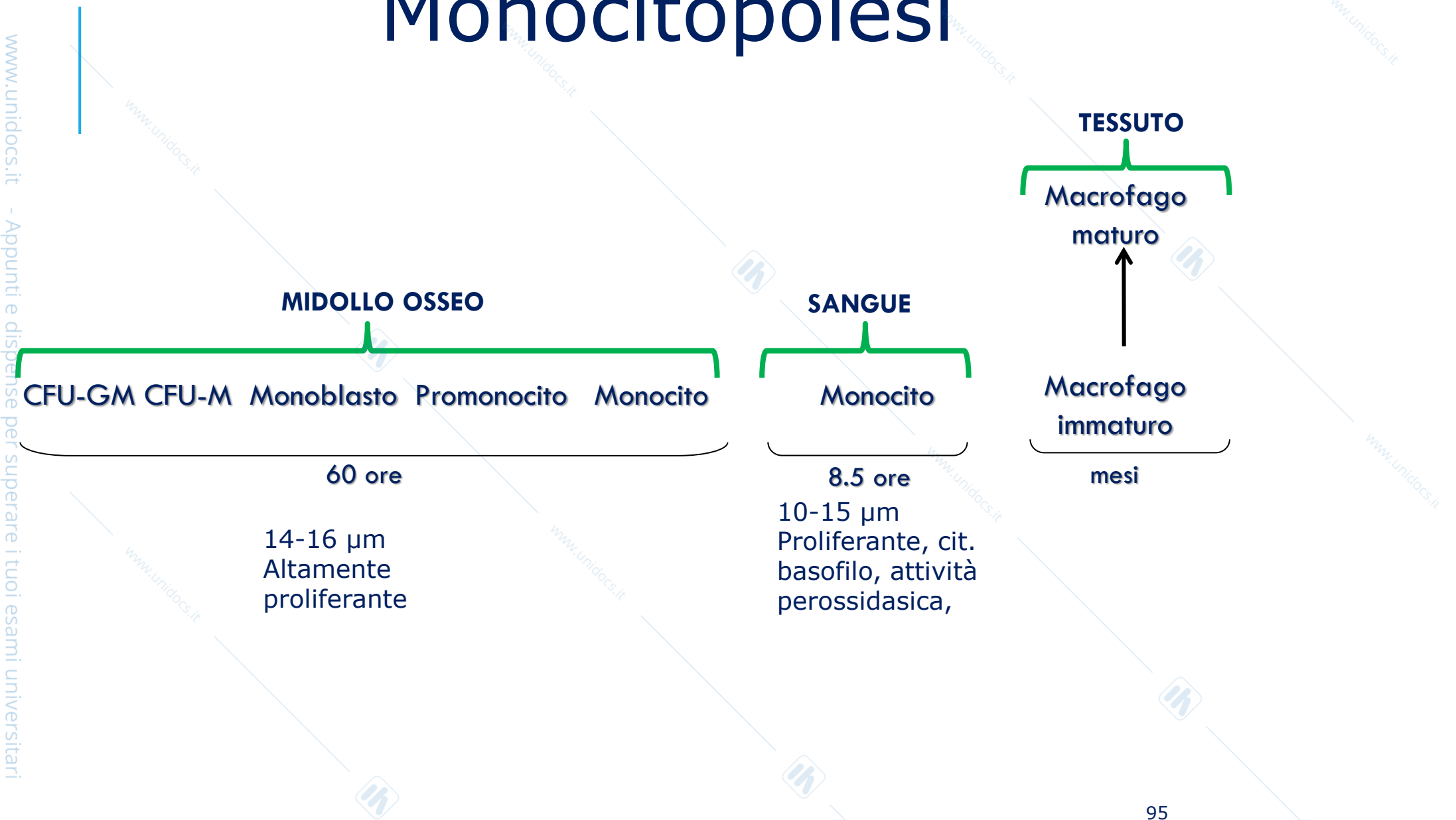


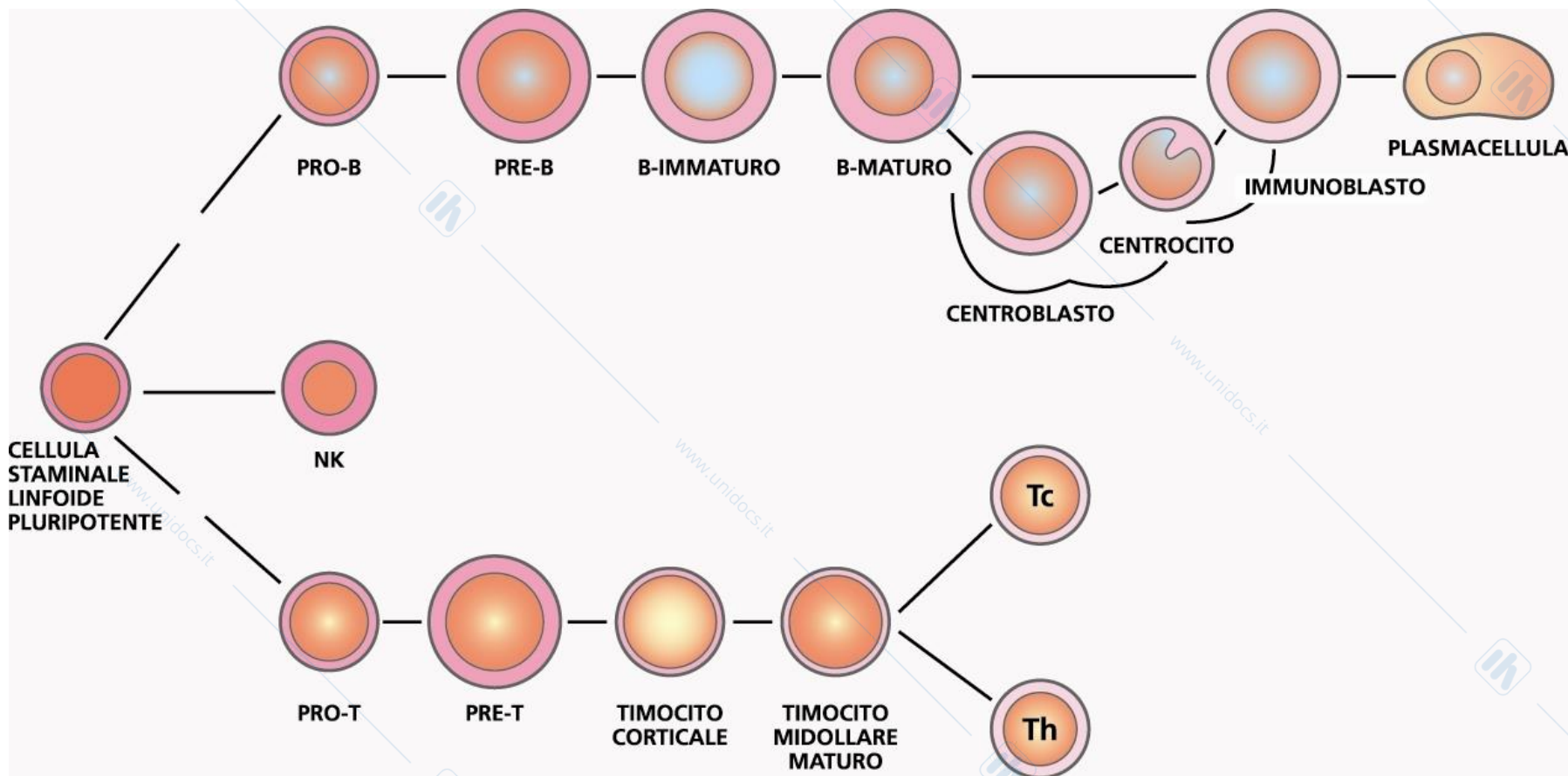
Basofilo

Linea Mieloide: Granulociti

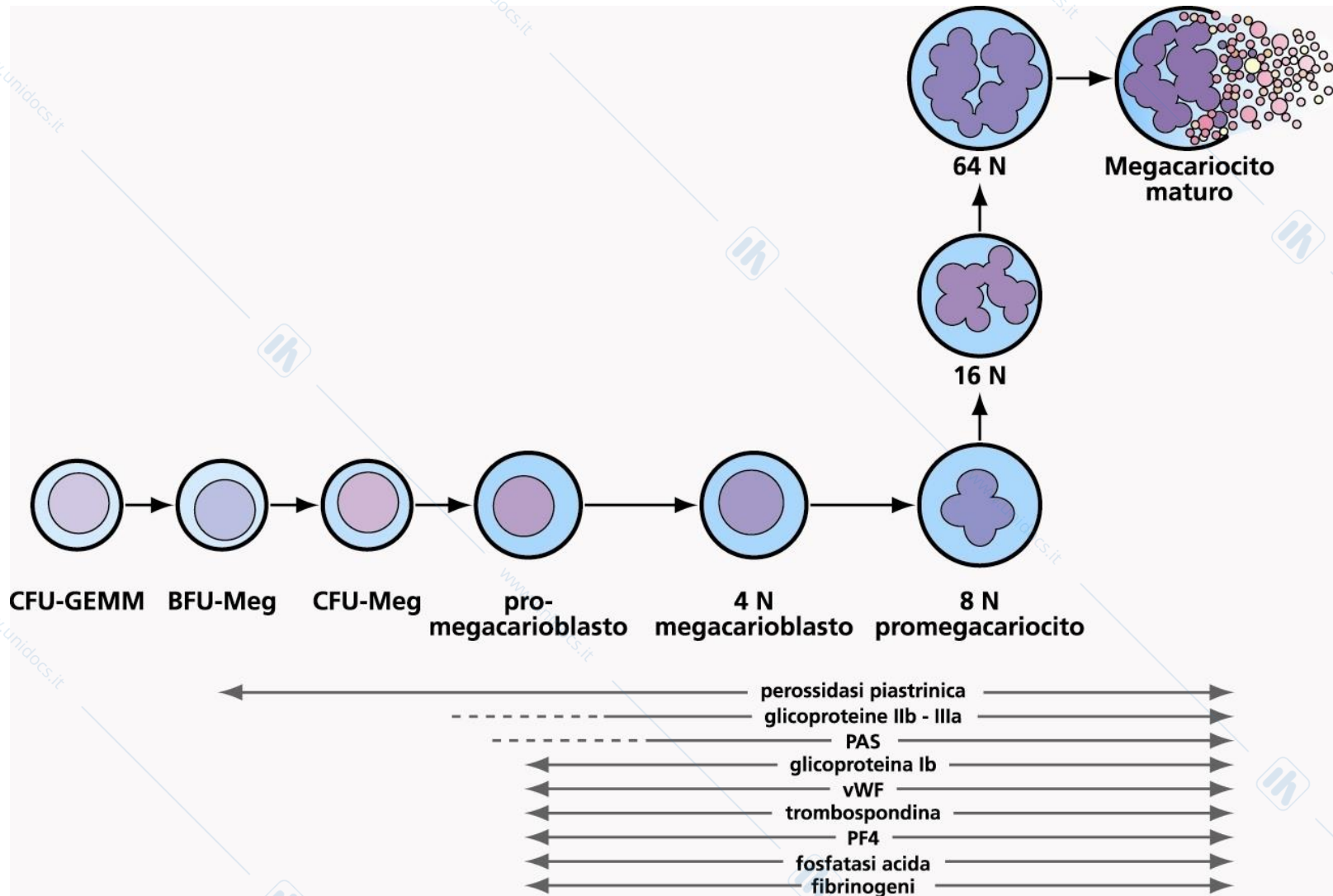


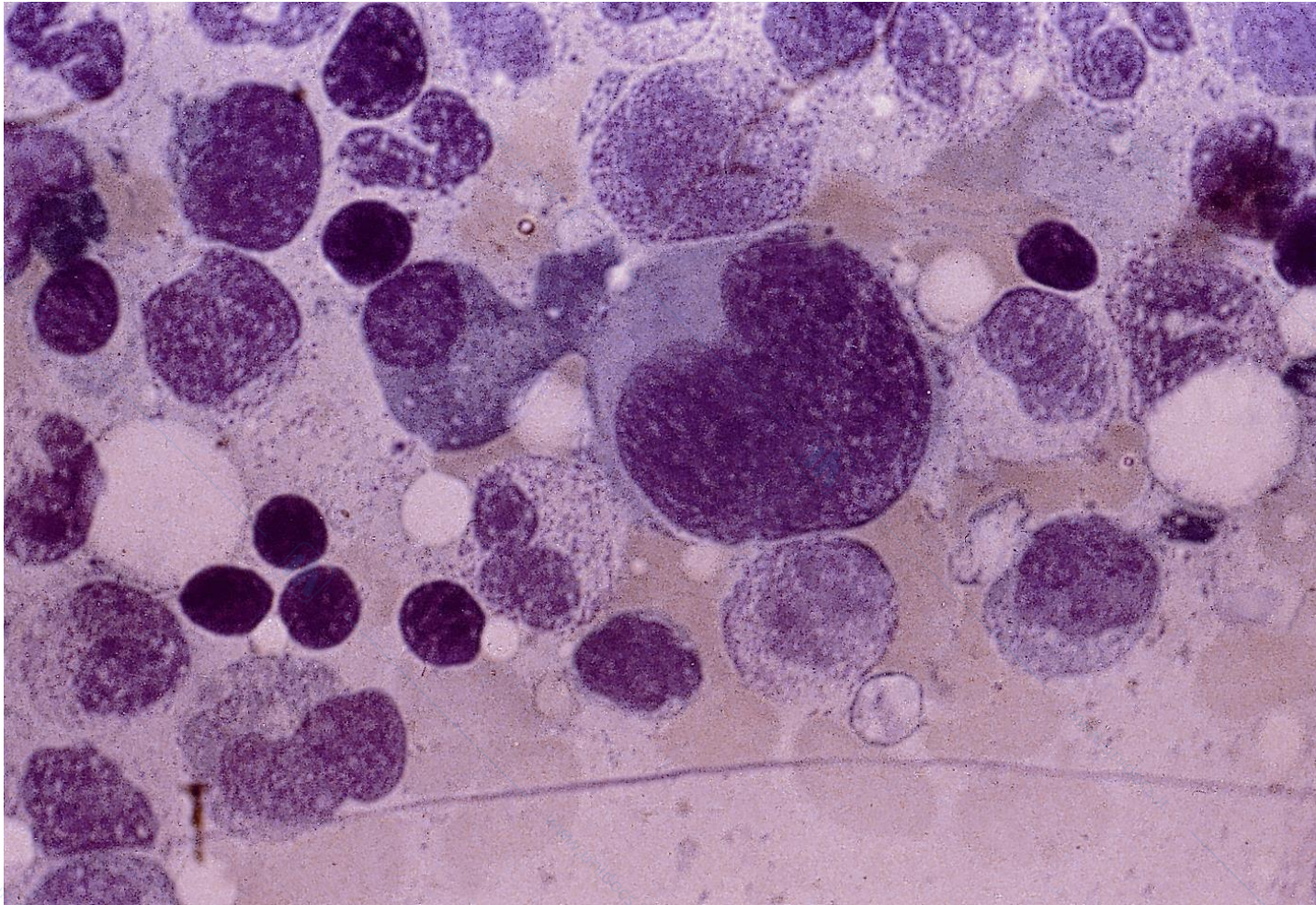
Monocitopoiesi





TROMBOCITOPOIESI





**Aspirato midollare:
megacarioblasto (40 μ m)**

REGOLAZIONE DELL'EMOPOIESI

- Regolazione locale
 - Fattori locali e CSF
- Regolazione sistemica
 - Eritropoietina prodotta dal rene
 - Trombopietina prodotta dal fegato