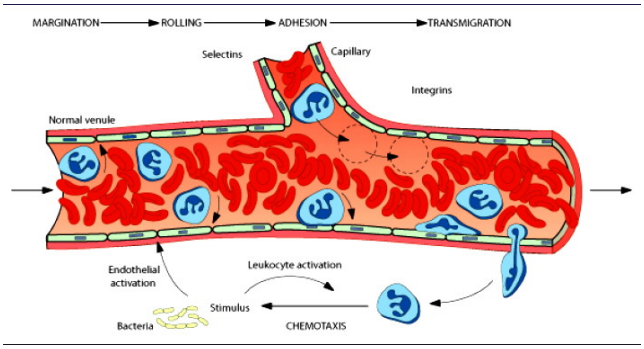
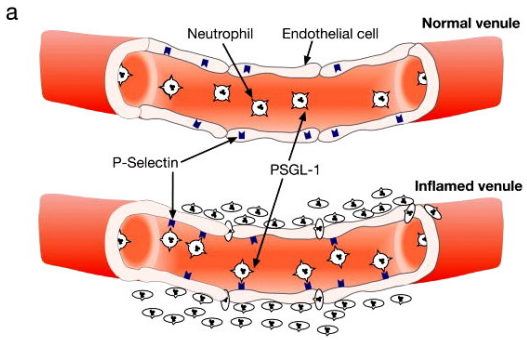


Molecole di adesione

Integrine
3. Estravasione dei leucociti

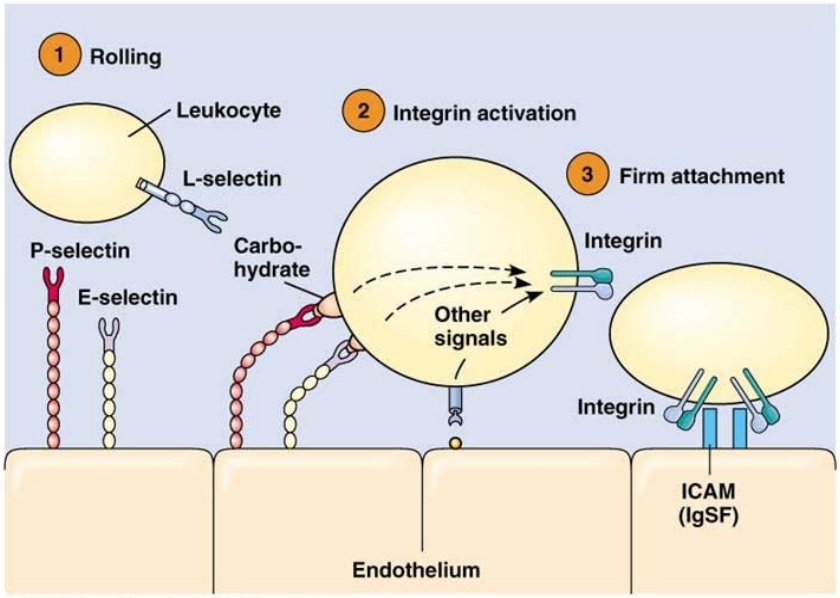
Filmato mostrato a lezione:
https://www.youtube.com/watch?v=HiJ_tcQJUwM

Ancoraggio dei leucociti circolanti all'endotelio attivato mediante interazioni fra selettine e i loro ligandi

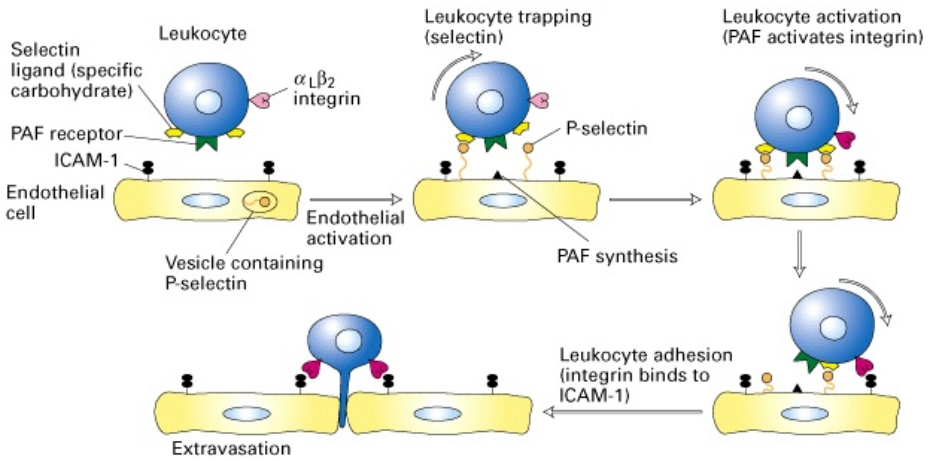


http://image.slidesharecdn.com/respuestainflamatoria-131114001039-phpapp01/95/respuesta-inflamatoria-inmunologia-10-638.jpg?cb=1384387886

(a) Nelle **venule normali** i leucociti fluiscono senza interazioni adesive con l'endotelio, ma nei **vasi infiammati**, vengono **espresse sulla superfice delle cellule endoteliali selettine e ligandi per le integrine**. Questo porta all'ancoraggio, rottolamento ("rolling"), e arresto dei leucociti circolanti e la loro finale estravasione dalla circolazione verso il tessuto circostante. Ad esempio, la P-selettina è normalmente espressa nei **corpi di Weibel-Palade** delle **cellule endoteliali**, ma entro pochi minuti dopo l'attivazione delle cellule endoteliali (mediante trombina, istamina, ipossia o danno), questi corpi si fondono con la membrana plasmatica, promuovendo **l'espressione della P-selettina sulla superficie della cellula endoteliale**. Allo stesso modo, la P-selettina immagazzinata nei **granuli α** delle **piastrine** viene espressa sulla superficie delle piastrine pochi minuti dopo l'attivazione piastrinica. **I leucociti si ancorano e rottolano sulle cellule endoteliali attivate e le piastrine.**



Le selectine, le ICAMs, e le integrine mediano l'adesione tra leucociti e cellulo endoteliali vicino ai siti di infezione



http://www.ncbi.nlm.nih.gov/books/NBK21599/figure/A6507/?report=objectonly

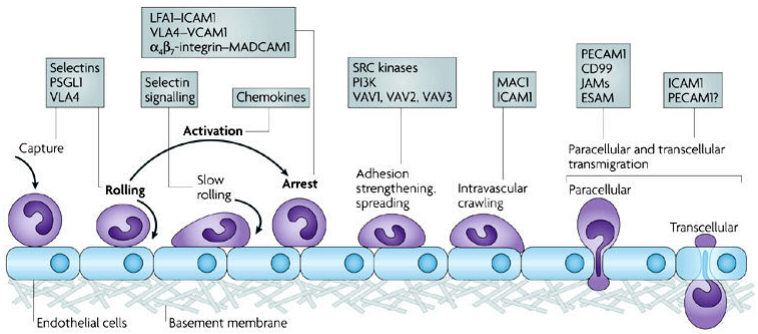
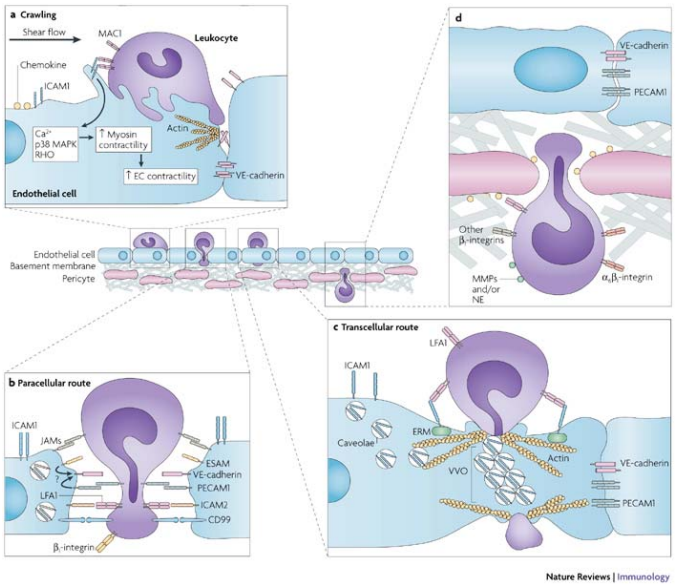


Figure 1 | **The updated leukocyte adhesion cascade.** The original three steps are shown in bold: rolling, which is mediated by selectins, activation, which is mediated by chemokines, and arrest, which is mediated by integrins. Progress has been made in defining additional steps: capture (or tethering), slow rolling, adhesion strengthening and spreading, intravascular crawling, and paracellular and transcellular transmigration. Key molecules involved in each step are indicated in boxes. ESAM, endothelial cell-selective adhesion molecule; ICAM1, intercellular adhesion molecule 1; JAM, junctional adhesion molecule; LFA1, lymphocyte function-associated antigen 1 (also known as $\alpha_L\beta_2$-integrin); MAC1, macrophage antigen 1; MADCAM1, mucosal vascular addressin cell-adhesion molecule 1; PSGL1, P-selectin glycoprotein ligand 1; PECAM1, platelet/endothelial-cell adhesion molecule 1; PI3K, phosphoinositide 3-kinase; VCAM1, vascular cell-adhesion molecule 1; VLA4, very late antigen 4 (also known as $\alpha_4\beta_1$-integrin).

Ley K, Laudanna C, Cybulsky MI, Nourshargh S. **Getting to the site of inflammation: the leukocyte adhesion cascade updated**. Nat Rev Immunol. 2007 Sep;7(9):678-89.
http://www.nature.com/nri/journal/v7/n9/images/nri2156-f1.jpg

Trasmigrazione



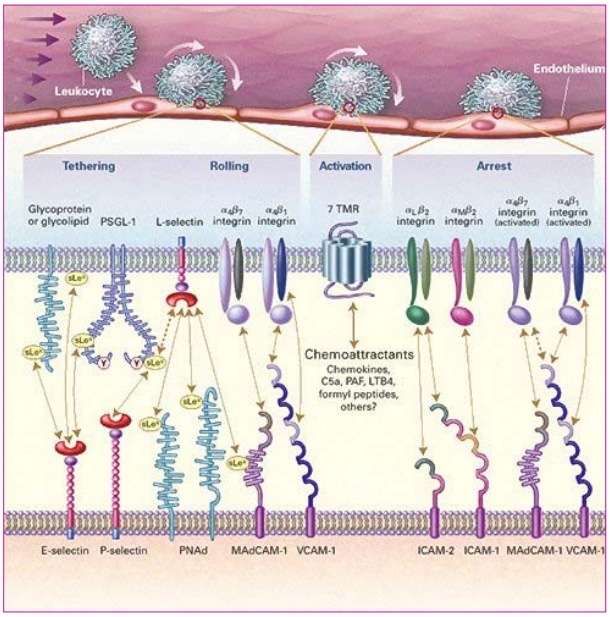
Vedi didascalia

Ley K, Laudanna C, Cybulsky MI, Nourshargh S. **Getting to the site of inflammation: the leukocyte adhesion cascade updated**. Nat Rev Immunol. 2007 Sep;7(9):678-89.
http://www.nature.com/nri/journal/v7/n9/images/nri2156-f3.jpg

Didascalia Figura Ley, 2007

Figure 3 | **Transmigration.** Migration of leukocytes through venular walls involves penetrating the endothelial-cell barrier and its associated basement membrane and the pericyte sheath. **a** | Extension of leukocyte membrane protrusions into the endothelial-cell body and endothelial-cell junctions is triggered by ligation of intercellular adhesion molecule 1 (ICAM1) by MAC1 (macrophage antigen 1). Ligation of ICAM1 is associated with increased intracellular Ca^{2+} and activation of p38 mitogen-activated protein kinase (MAPK) and RAS homologue (RHO) GTPase, which may collectively activate myosin light-chain kinase leading to enhanced endothelial-cell contraction and hence opening of interendothelial contacts. These events may promote leukocyte migration through endothelial junctions (paracellular route), although leukocyte migration can also occur through the body of the endothelium (transcellular route). Transmigration through the endothelium can also induce cell-surface expression of members of the β_1-integrin family and proteases on neutrophils and other leukocytes that may facilitate the onwards movement of the leukocyte through the vessel wall. **b** | Paracellular migration involves the release of endothelial-expressed vascular endothelial cadherin (VE-cedherin) and is facilitated by intracellular membrane compartments containing a pool of platelet/endothelial-cell adhesion molecule 1 (PECAM1) and possibly other endothelial-cell junctional molecules, such as junctional adhesion molecule A (JAM-A). Other molecules involved in paracellular transmigration are endothelial cell-selective adhesion molecule (ESAM), ICAM2 and CD99. **c** | Transcellular migration occurs in 'thin' parts of the endothelium, and therefore there is less distance for a leukocyte to migrate. ICAM1 ligation leads to translocation of ICAM1 to actin- and caveolae-rich regions. ICAM1-containing caveolae link together forming vesiculo-vacuolar organelles (VVOs) that form an intracellular channel through which a leukocyte can migrate. Ezrin, radixin and moesin (ERM) proteins could act as linkers between ICAM1 and cytoskeletal proteins (such as actin and vimentin), causing their localization around the channel, thereby providing structural support for the cell under these conditions. **d** | Migration through the endothelial basement membrane and pericyte sheath can occur through gaps between adjacent pericytes and regions of low protein deposition within the extracellular matrix. This response can be facilitated by $\alpha_v\beta_1$-integrin and possibly proteases, such as matrix metalloproteinases (MMPs) and neutrophil elastase (NE). ERM, ezrin, radixin and moesin; LFA1, lymphocyte function-associated antigen 1.

Ley K, Laudanna C, Cybulsky MI, Nourshargh S. **Getting to the site of inflammation: the leukocyte adhesion cascade updated**. Nat Rev Immunol. 2007 Sep;7(9):678-89.
http://www.nature.com/nri/journal/v7/n9/fig_tab/nri2156_F3.html#figure-title



http://www.med.monash.edu.au/assets/images/immunology/lab-heads/imm-inflame.jpg

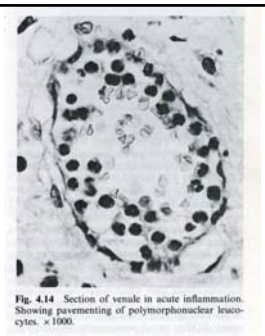
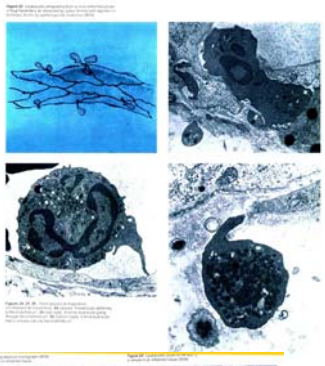
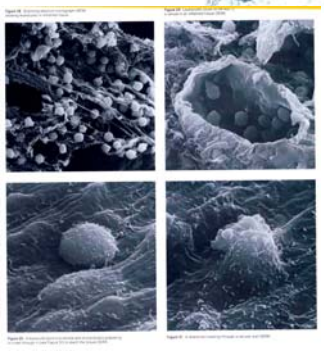
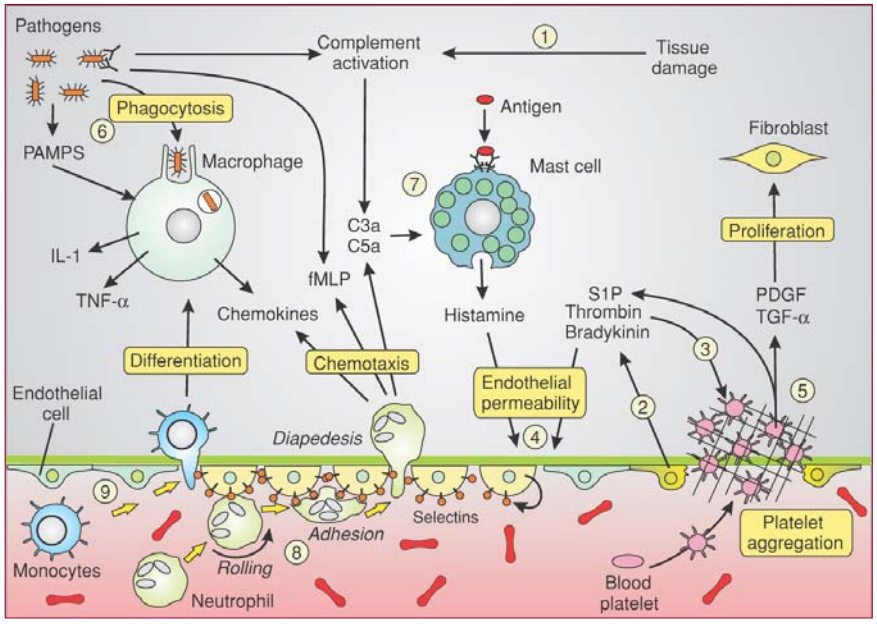


Fig. 4.14 Section of venule in acute inflammation. Showing pavementing of polymorphonuclear leucocytes. × 1000.

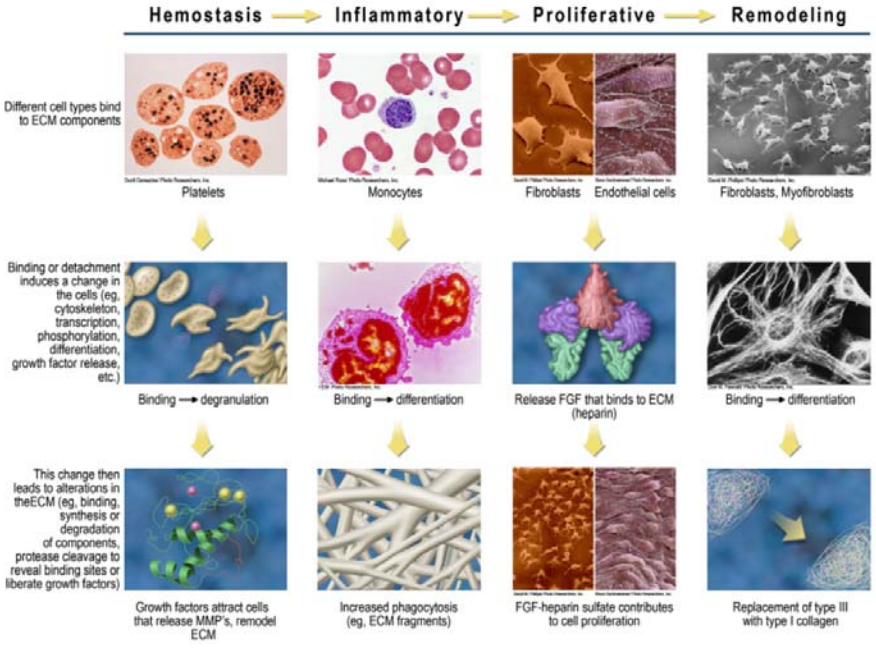


- L'**estravasione** dei **leucociti** è un importante processo sia nei meccanismi di auto-difesa nei siti di infiammazione che nel processo di "homing" dei linfociti verso gli organi linfoidi secondari.
- E' inoltre importante come processo responsabile della patogenesi dei disturbi infiammatori.





Cell Signalling Biology - Michael J. Berridge - www.cellsignallingbiology.org - 2009



Schultz et al**: Dynamic reciprocity in the wound microenvironment**. Wound Repair Regen. 19:134-148, 2011.

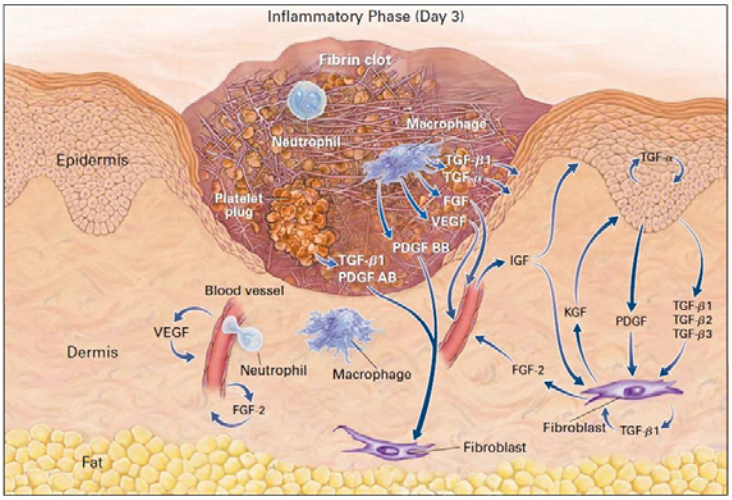


Figure 1. A Cutaneous Wound Three Days after Injury.
Growth factors thought to be necessary for cell movement into the wound are shown. TGF-β1, TGF-β2, and TGF-β3 denote transforming growth factor β1, β2, and β3, respectively; TGF-α transforming growth factor α; FGF fibroblast growth factor; VEGF vascular endothelial growth factor; PDGF, PDGF AB, and PDGF BB platelet-derived growth factor, platelet-derived growth factor AB, and platelet-derived growth factor BB, respectively; IGF insulin-like growth factor; and KGF keratinocyte growth factor.

Singer AJ, Clark RA. **Cutaneous wound healing**. N Engl J Med. 341:738-746, 1999.

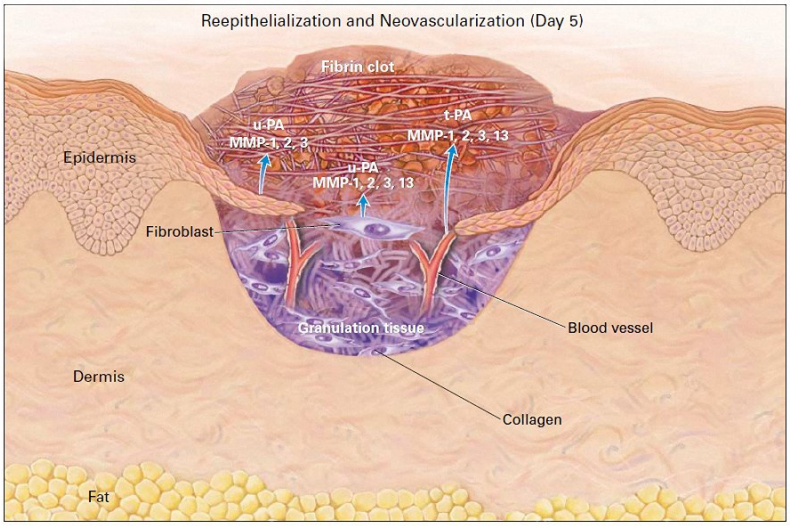
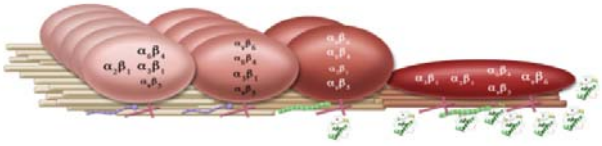


Figure 2. A Cutaneous Wound Five Days after Injury.
Blood vessels are seen sprouting into the fibrin clot as epidermal cells resurface the wound. Proteinases thought to be necessary for cell movement are shown. The abbreviation u-PA denotes urokinase-type plasminogen activator; MMP-1, 2, 3, and 13 matrix metalloproteinases 1, 2, 3, and 13 (collagenase 1, gelatinase A, stromelysin 1, and collagenase 3, respectively); and t-PA tissue plasminogen activator.

Singer AJ, Clark RA. **Cutaneous wound healing**. N Engl J Med. 341:738-746, 1999.



Schultz GS, Davidson JM, Kirsner RS, Bornstein P, Herman IM. **Dynamic reciprocity in the wound microenvironment**. Wound Repair Regen. 2011 Mar-Apr;19(2):134-48.

Integrin switching helps mediate ***keratinocyte migration across wounded skin***. In this graphic representation, keratinocytes are depicted as ovals containing the major integrin subunits they express, and the extracellular matrix is depicted as elongated brown cylinders. Intact keratinocytes bound to basement membrane are shown on the left and migrating keratinocytes at the wound edge are shown on the right. Matrix metalloproteases (MMPs) enable migration by breaking down the underlying basal lamina at the leading edge of the keratinocyte sheet, where the cells assume a flattened shape and express an array of integrins that permits migration across the newly formed granulation tissue. The leading epithelial cells rearrange their distribution of b1 integrins to engage with type I collagen below the damaged/absent basement membrane.