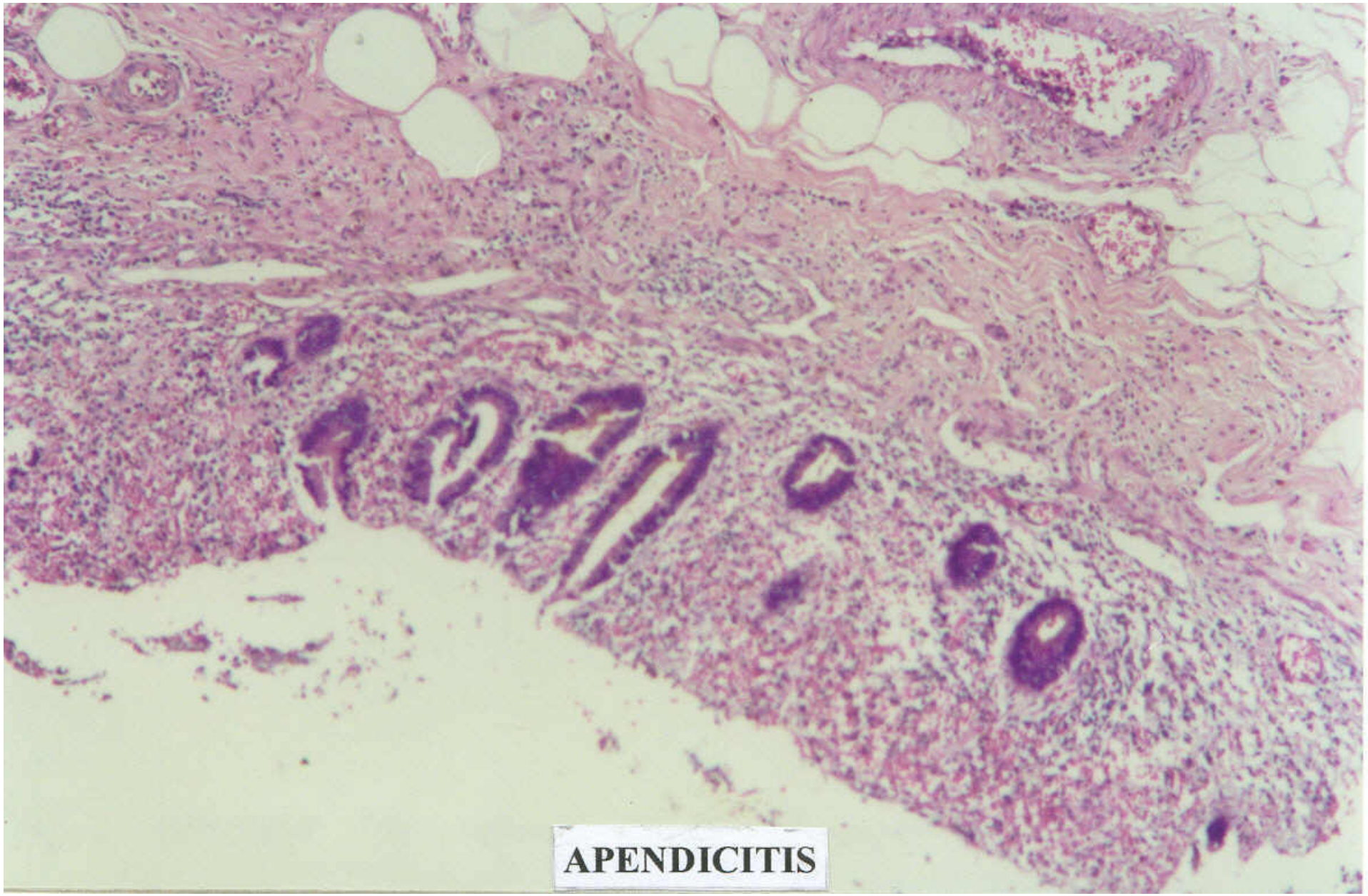
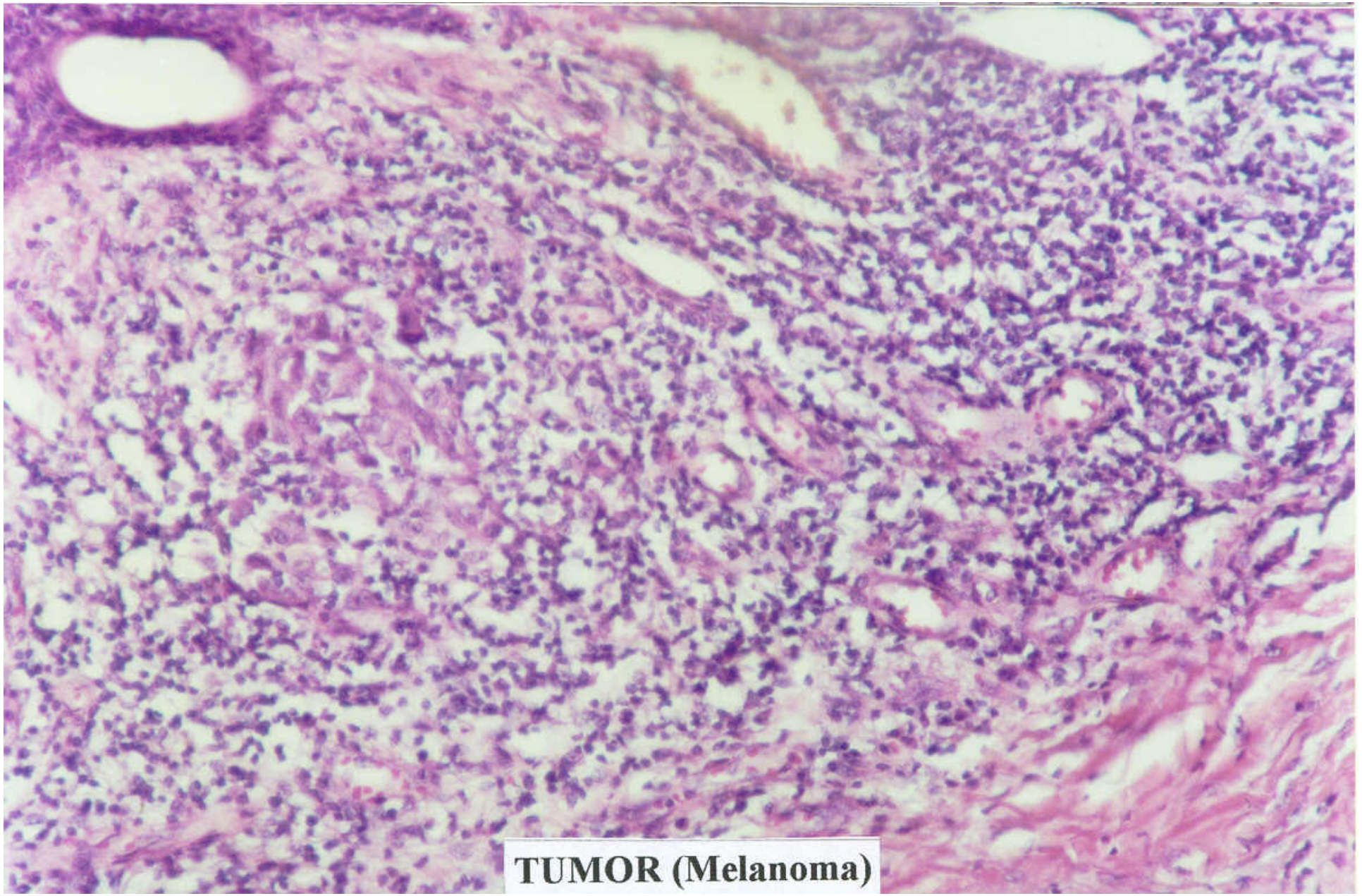
CITOQUINAS

MOLÉCULAS DE ADHESIÓN


APENDICITIS


TUMOR (Melanoma)

Inflammatory Changes after Cryosurgery-Induced Necrosis in Human Melanoma Xenografted in Nude Mice

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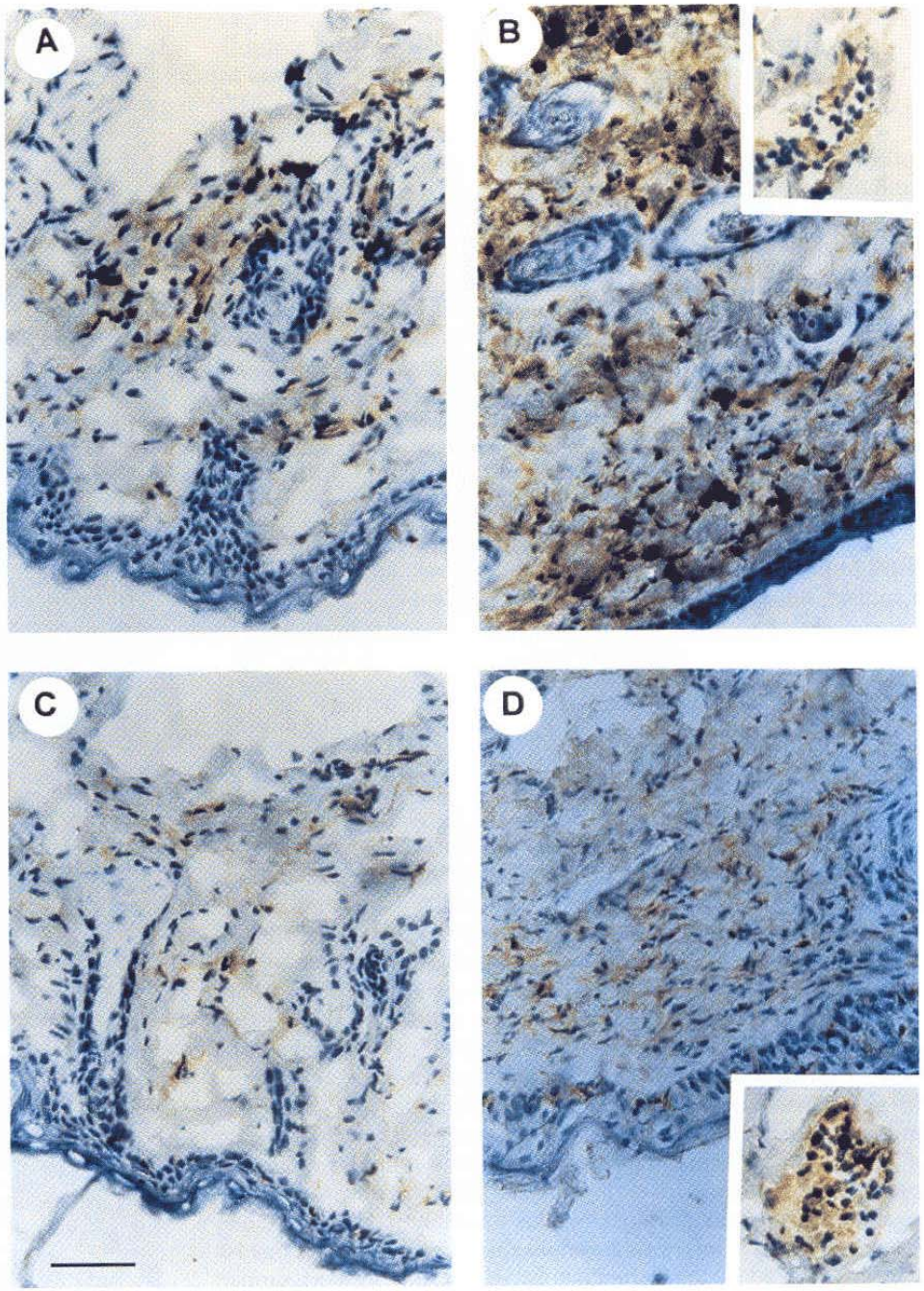
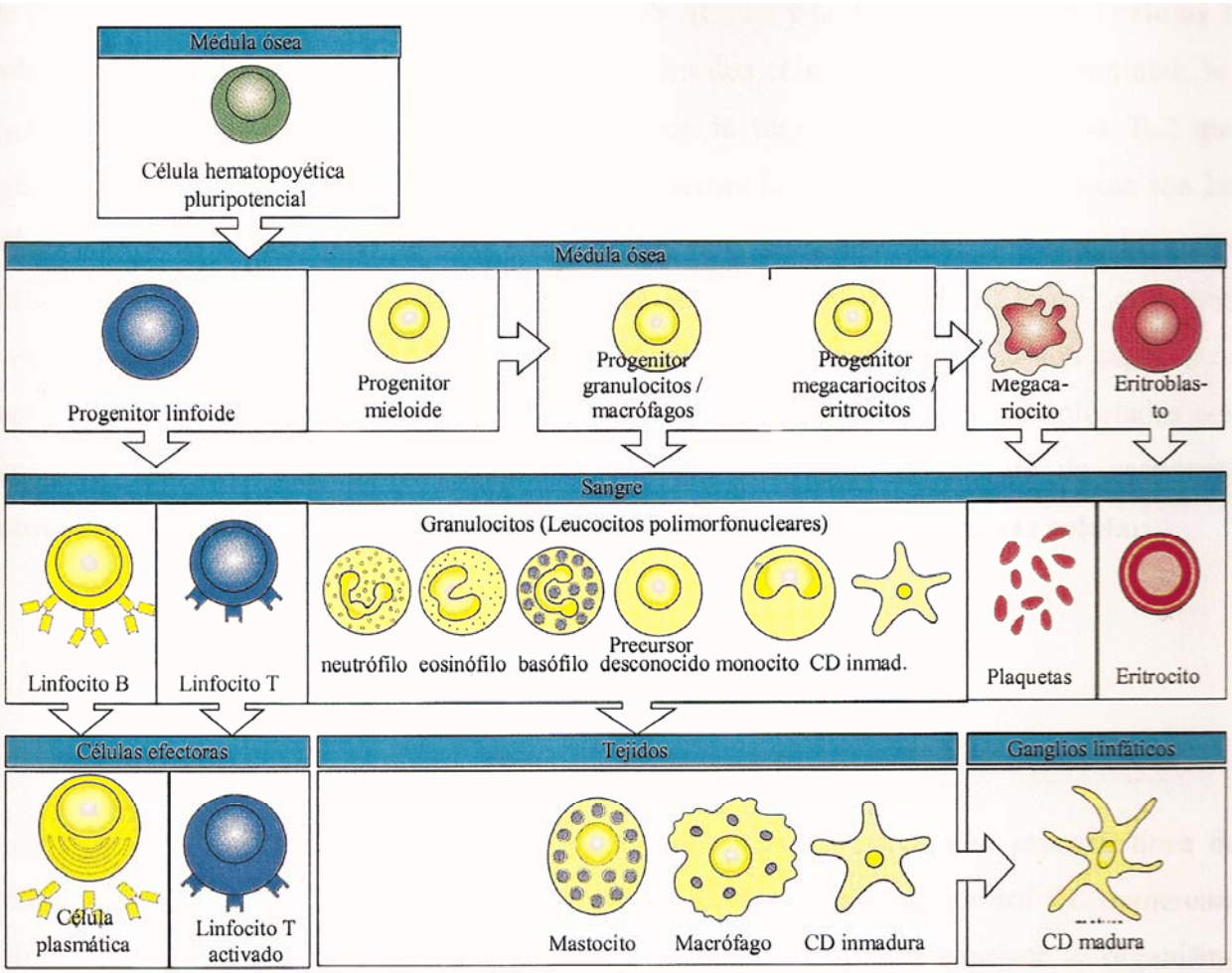
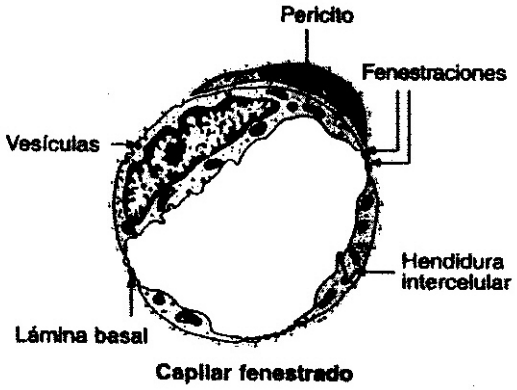


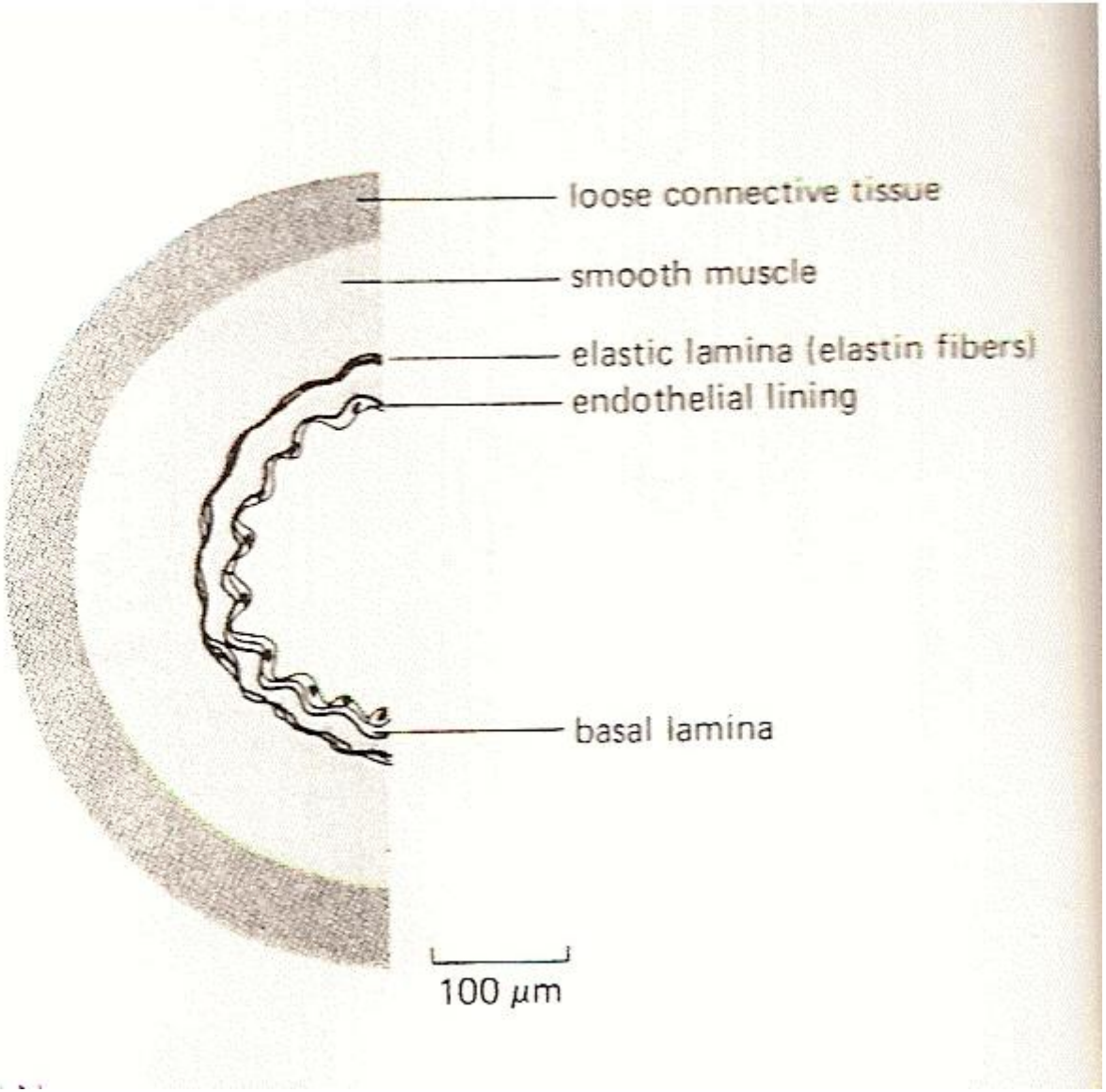
Figure 1. Comparative analysis of macrophages and DC populations 3 d post-treatment. (A) Immunohistochemical detection for F4/80-positive macrophages in the tumor-adjacent dermis from a group I mouse. (B) A representative area from a group IV mouse showing the peritumoral adjacent dermis densely populated with F4/80-positive cells. *Inset*: F4/80-negative inflammatory cells at the lumen of a dermic vessel. (C) Immunohistochemical staining for DEC 205-positive cells performed in consecutive sections from the same tumor depicted in (*A*). (D) an increased number of DC close to necrotic areas is observed in peritumoral dermis from a group IV mouse. *Inset*: Cells within the same vessel as in (*B*) demonstrate intense positivity for DEC 205. *Scale bar*: 2.5 μm; *insets*, 2.27 μm.

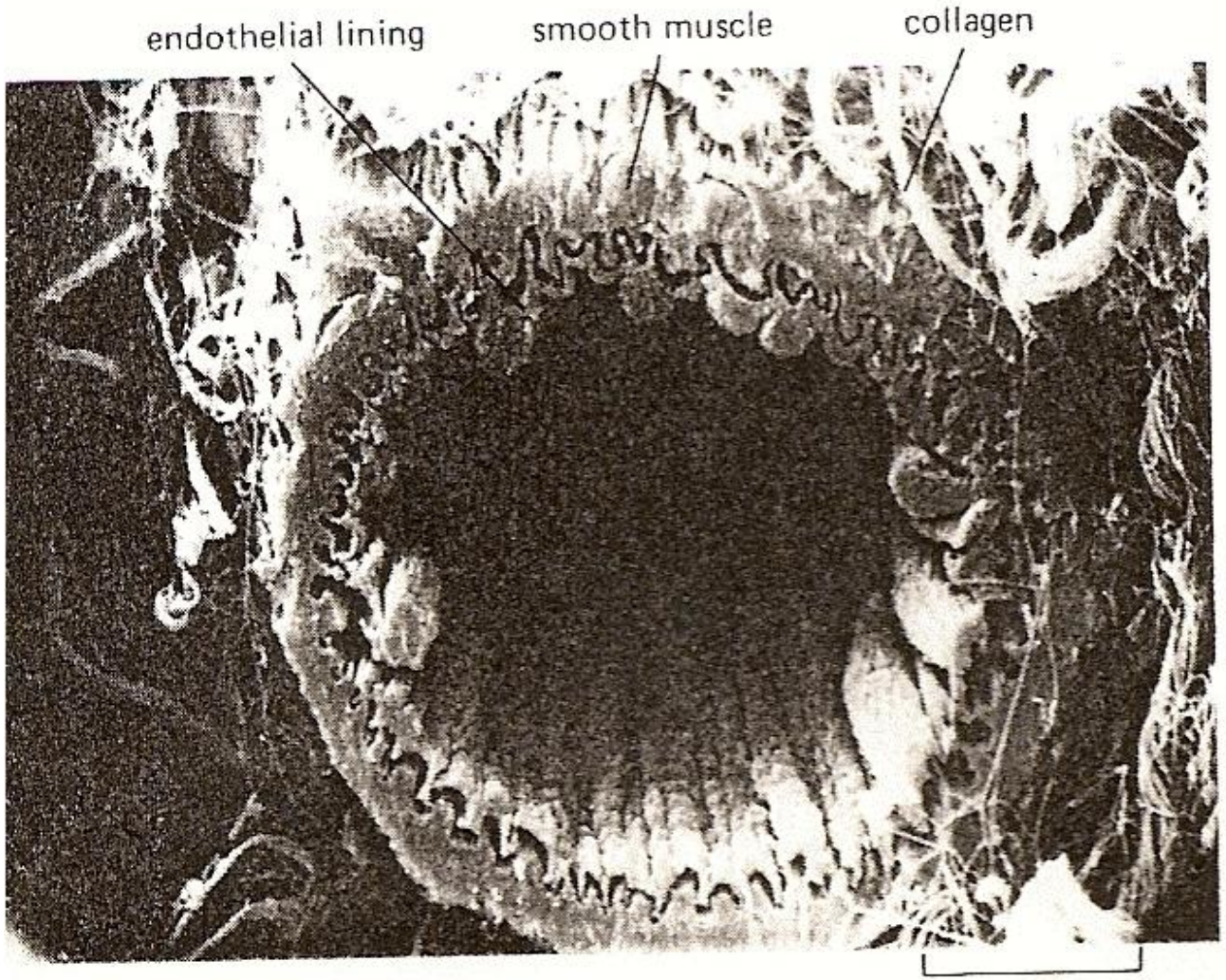


Esquema 1 Todos los elementos celulares de la sangre, incluyendo los linfocitos del sistema inmune adaptativo, provienen de células hematopoyéticas de la médula ósea (Adaptado de Immunobiology 5th edn, Janeway C.)



Sección transversal de un capilar [Tomado de Genesser, 2000]


loose connective tissue
smooth muscle
elastic lamina (elastin fibers)
endothelial lining
basal lamina
100 μm



(B)

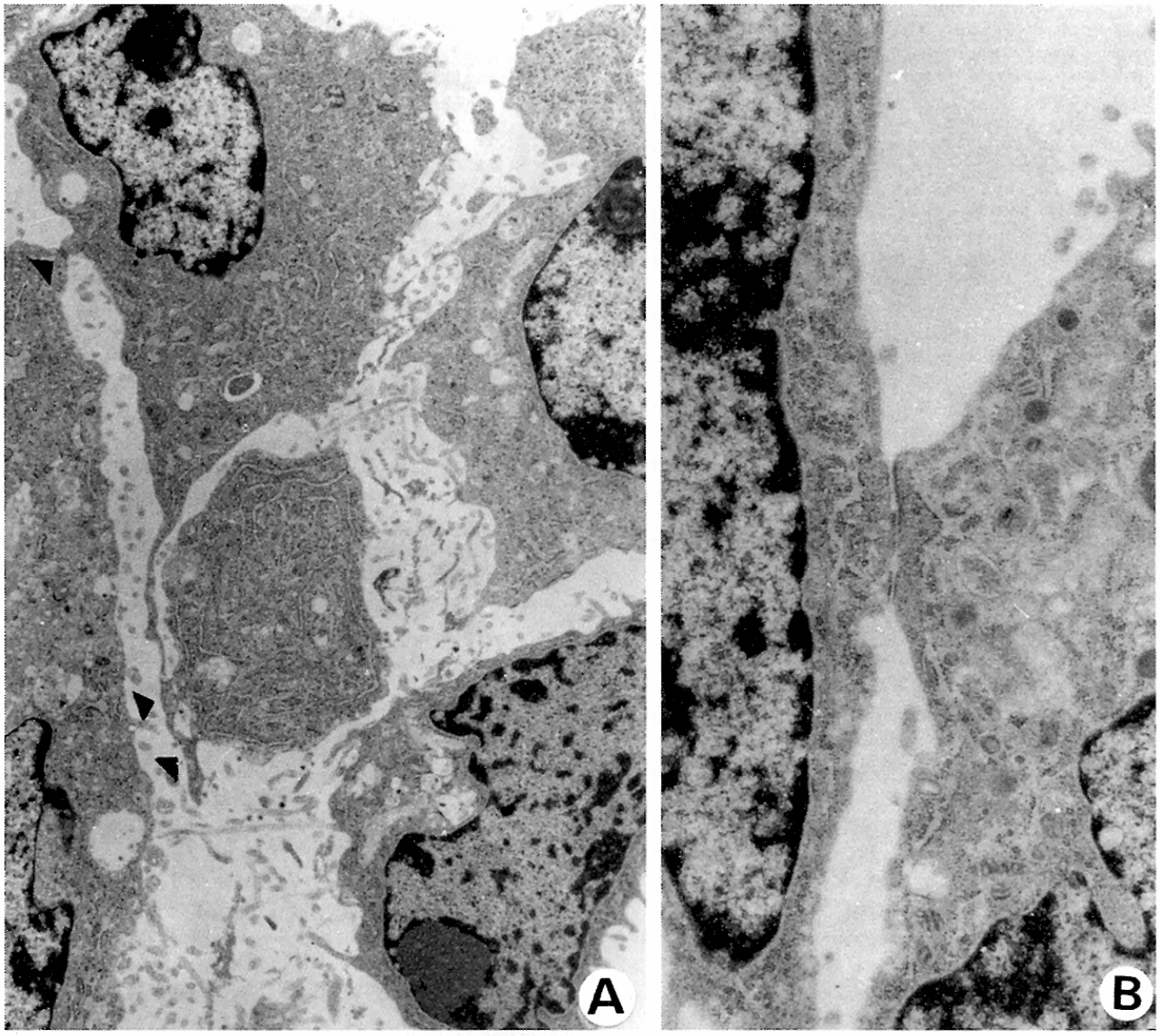
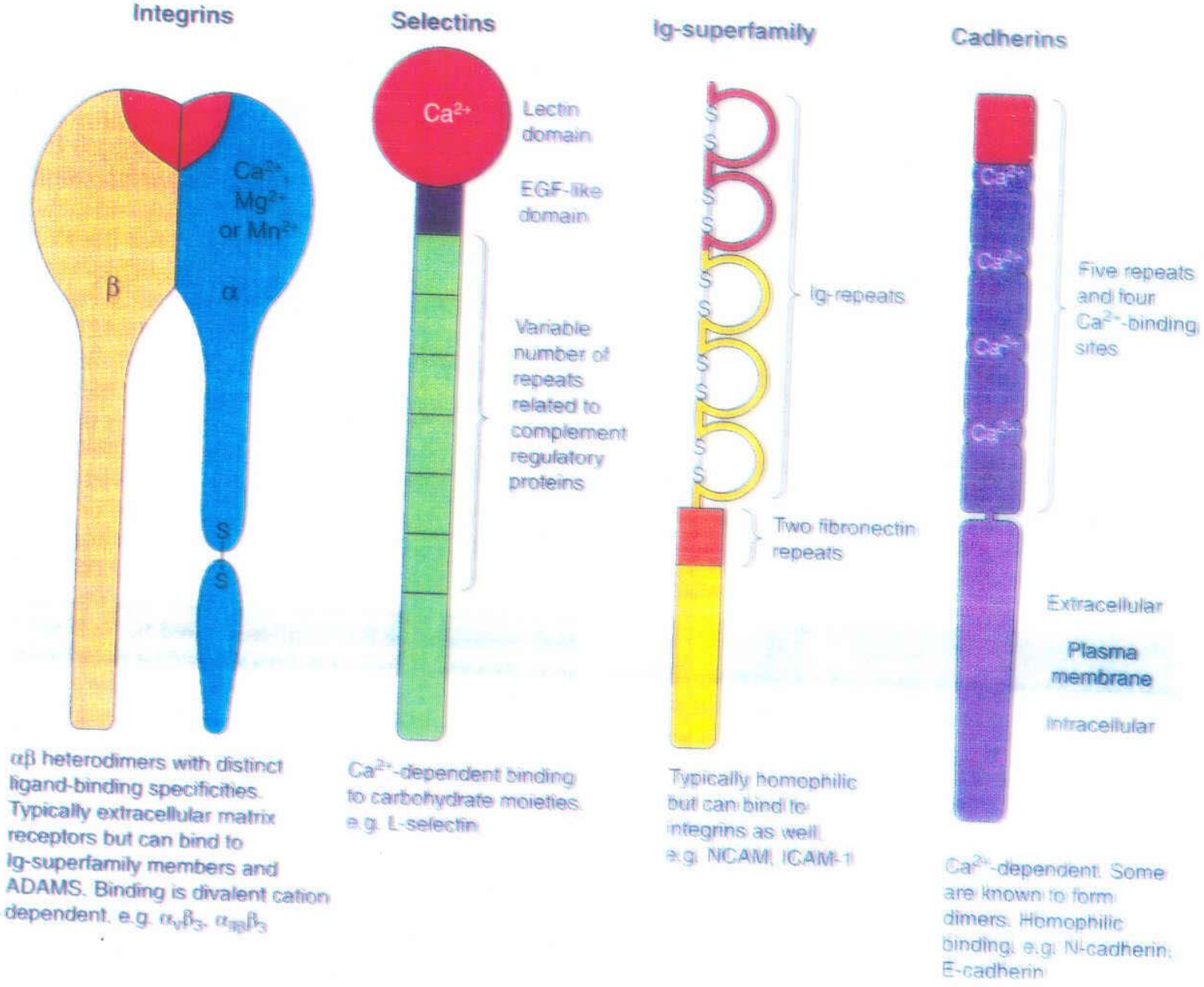


FIG. 5. Electron micrograph of REC-A4 cells in culture. (*A*) REC-A4 cells in culture are connected to each other by junctions. Each cell contains many vesicles, probably pinocytic, but no Weibel–Palade bodies in its cytoplasm. Original magnification: ×4000. *Scale bar*: 1 cm = 1.43 μm. (*B*) Electron micrograph of a contact between two REC-A4 cells. *Scale bar*: 1 cm = 0.64 μm.

Major classes of cell-adhesion receptors

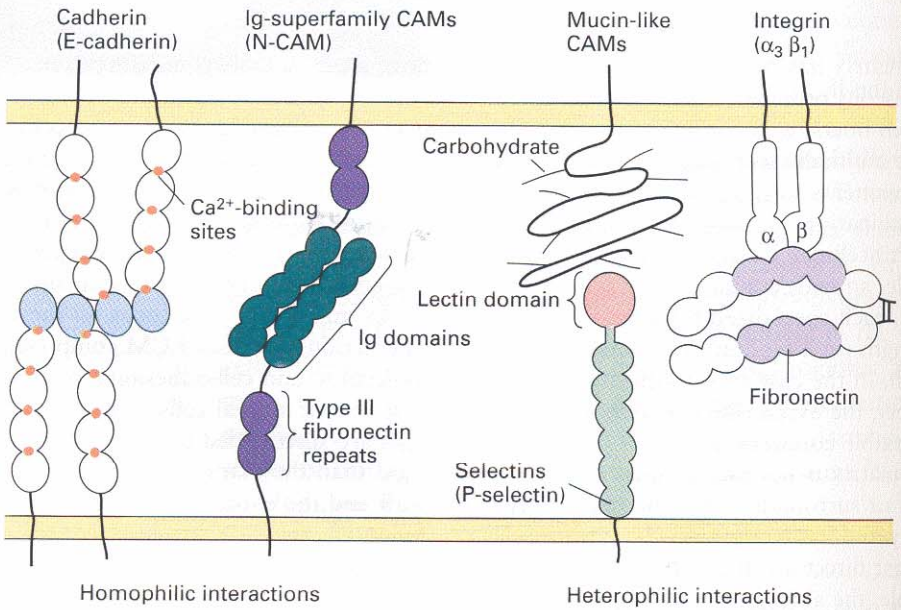


αβ heterodimers with distinct ligand-binding specificities. Typically extracellular matrix receptors but can bind to Ig-superfamily members and ADAMS. Binding is divalent cation dependent. e.g. $\alpha_V\beta_3$, $\alpha_{IIb}\beta_3$

Ca^{2+}-dependent binding to carbohydrate moieties. e.g. L-selectin

Typically homophilic but can bind to integrins as well. e.g. NCAM, ICAM-1

Ca^{2+}-dependent. Some are known to form dimers. Homophilic binding. e.g. N-cadherin, E-cadherin



▲ FIGURE 22-2 Major families of cell-adhesion molecules (CAMs). Integral membrane proteins are built of multiple domains. Cadherin and the immunoglobulin (Ig) superfamily of CAMs mediate homophilic cell-cell adhesion. For cadherin, calcium binding to sites (orange) between the five domains in the extracellular segment is necessary for cell adhesion; the N-terminal domain (blue) causes cadherin to dimerize and to bind cadherin dimers from the opposite membrane. The Ig superfamily contains multiple domains (green) similar in structure to immunoglobulins and frequently contain type III fibronectin repeats (purple). In a heterophilic interaction, the lectin domain of selectins binds carbohydrate chains in mucin-like CAMs on adjacent cells in the presence of Ca^{2+}. The lectin domain is separated from the membrane by a series of repeated domains. The major cell-matrix adhesion molecule, integrin, is a heterodimer of α and β subunits. They bind to the cell-binding domain of fibronectin, laminin, or other matrix molecules.

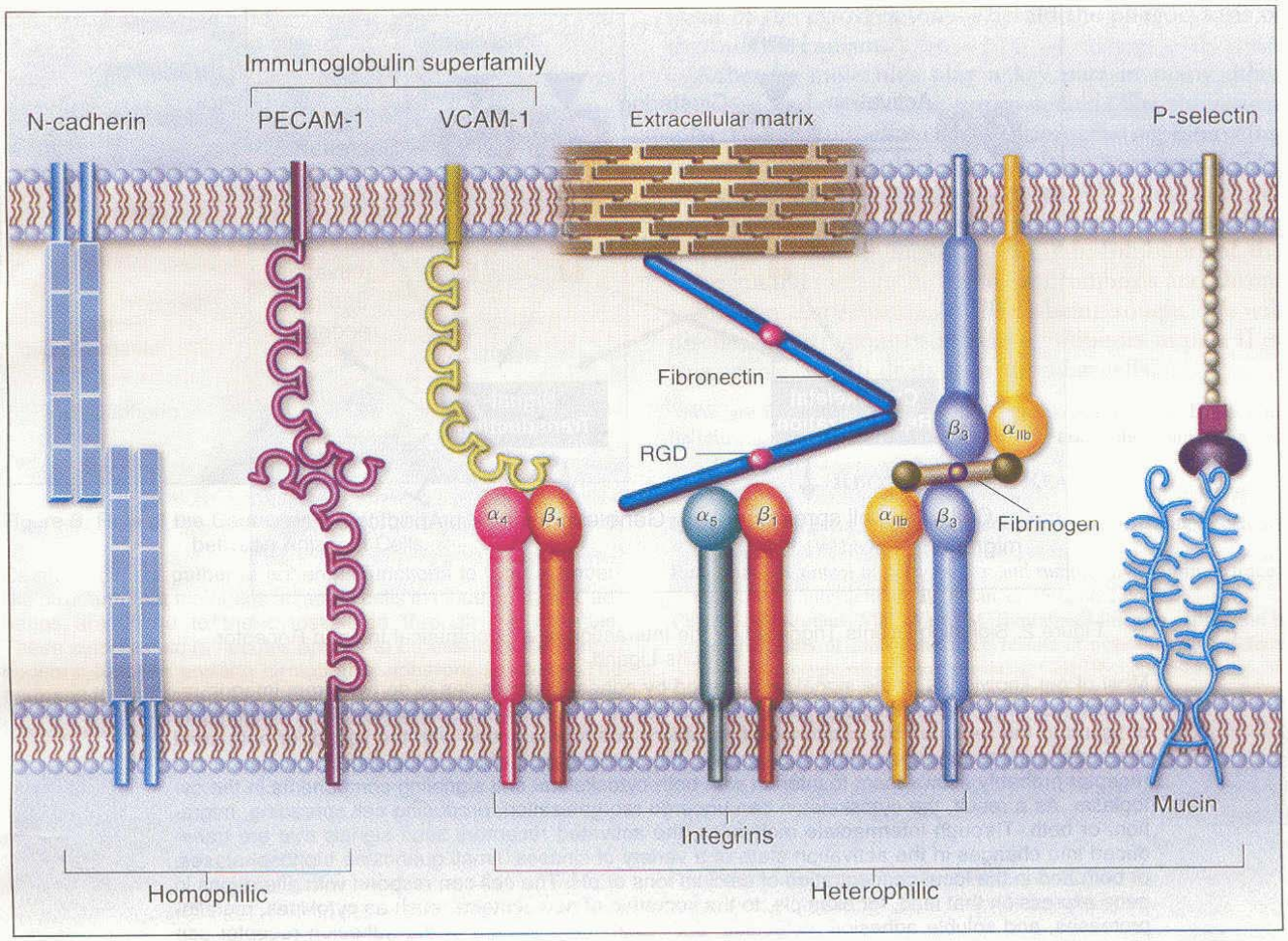


Figure 1. The Four Major Classes of Adhesion Receptors, Shown Embedded in a Putative Plasma Membrane.

Cadherins typically mediate a calcium-dependent, homophilic adhesion between cells. The crystal structure of the domains of these receptors suggests that adjacent molecules form dimers and interact with dimers on the opposite cell. N-cadherin is one of the adhesion molecules mediating the outgrowth of neurites. The second major class, the immunoglobulin superfamily, may also mediate homophilic interactions. The binding sites of these receptors are characteristically, but not always, in the two most distal domains. They mediate cell–cell adhesion that is not dependent on divalent cations. Platelet–endothelial-cell adhesion molecule 1 (PECAM-1), expressed also on leukocytes, appears to have a role in the migration of leukocytes across endothelium. Other members of the immunoglobulin superfamily mediate heterophilic interactions with integrins. For example, vascular-cell adhesion molecule 1 (VCAM-1) found on stimulated endothelial cells binds the $\alpha_4\beta_1$ or $\alpha_4\beta_7$ integrin on lymphocytes. Integrins, the third major class, are heterodimers whose two chains contribute to ligand binding, which requires the presence of divalent cations. Many integrins bind to proteins in the extracellular matrix, as shown with $\alpha_5\beta_1$, which is a receptor for fibronectin and can support the assembly of the fibronectin matrix. Integrins also bind soluble adhesion molecules, such as fibrinogen, which forms cross-links with the platelet integrin $\alpha_{IIb}\beta_3$ during platelet aggregation. A short motif in the amino acid sequence, such as arginine–glycine–aspartic acid (RGD), is often the primary site of recognition by the integrin receptor. Finally, the selectins, which have a distal calcium-dependent lectin domain, interact with carbohydrate groups on highly glycosylated protein ligands. P-selectin is found on activated platelets and endothelial cells and mediates adhesion to specific mucins present on many leukocytes.

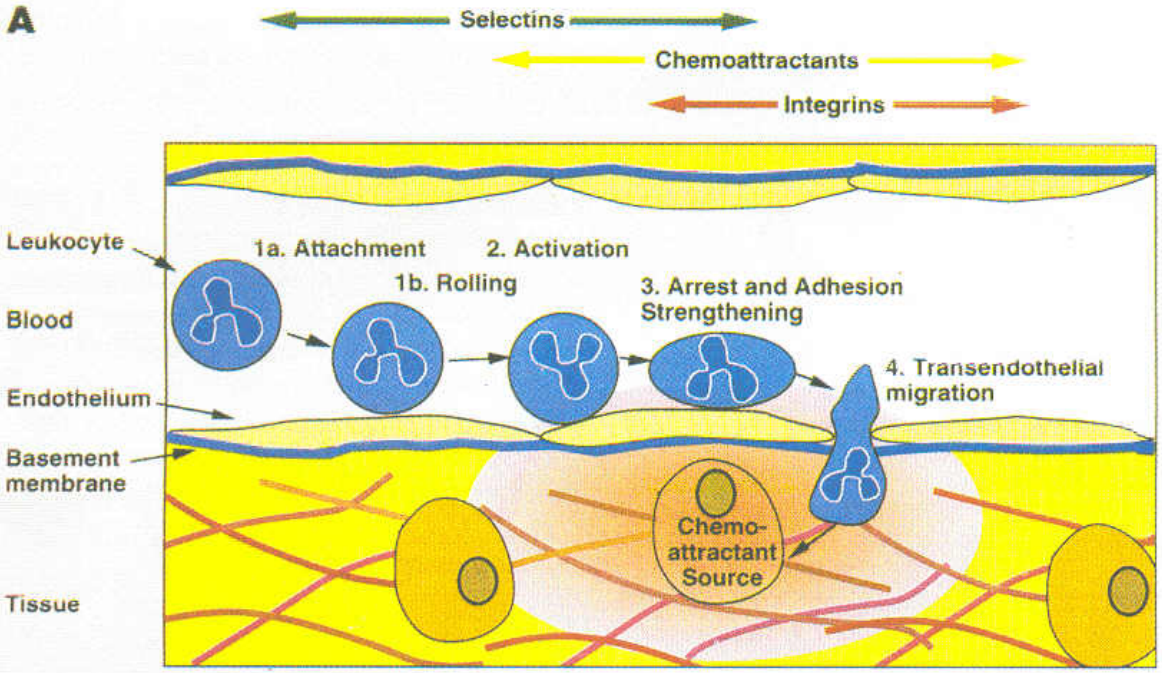


Figure 6. The Three-Step Area Code Model

(A) Selectins, chemoattractants, and integrins act in sequence, with some overlap.

(B) Combinatorial use of different molecules at each step can generate a large number of different area codes and specificity for distinct leukocyte subpopulations. All of the known selectin and integrin interactions are shown in the hundreds and ones place, respectively; however, owing to space limitations, only a subset of the chemoattractants is shown in the tens place (see Table 1). The area codes symbolize how specificity for monocytes, neutrophils, or both can be generated at inflammatory sites. Interactions that are monocyte or neutrophil specific are shown in blue and red, respectively.

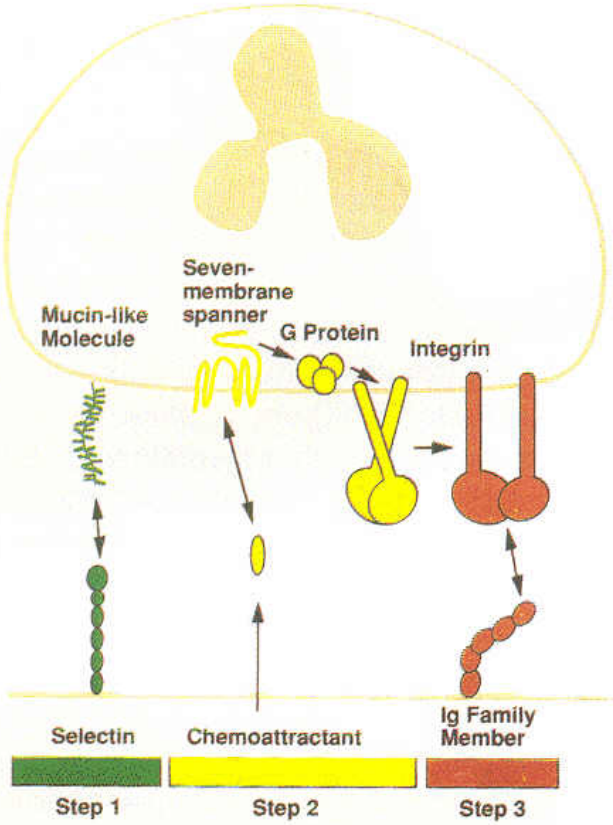


Figure 1. Three Sequential Steps Provide the Traffic Signals That Regulate Leukocyte Localization in the Vasculature

Selectin molecules that bind carbohydrate ligands, often displayed on mucin-like molecules, are responsible for the initial tethering of a flowing leukocyte to the vessel wall and for labile, rolling adhesions. Tethering brings leukocytes into proximity with chemoattractants that are displayed on or released from the endothelial lining of the vessel wall. Chemoattractants bind to receptors that span the membrane seven times on the surface of leukocytes. These couple to G proteins, which transduce signals that activate integrin adhesiveness. The integrins can then bind to IgSF members on the endothelium, increasing adhesiveness and resulting in arrest of the rolling leukocyte. Following directional cues from chemoattractants and using integrins for traction, leukocytes then cross the endothelial lining of the blood vessel and enter the tissue.

Transmigración de leucocitos

- La unión, el rodamiento y la adhesión de los leucocitos sobre la superficie de las células endoteliales involucran interacciones heterofílicas entre una clase de molécula sobre el leucocito y otra clase de molécula sobre la célula endotelial

Diapedesis

- Es un proceso rápido en el cual los leucocitos se extienden a través del borde endotelial por pseudopodos, donde al menos dos interacciones moleculares involucran interacciones homofílicas, PECAM-1/CD31 y CD 99

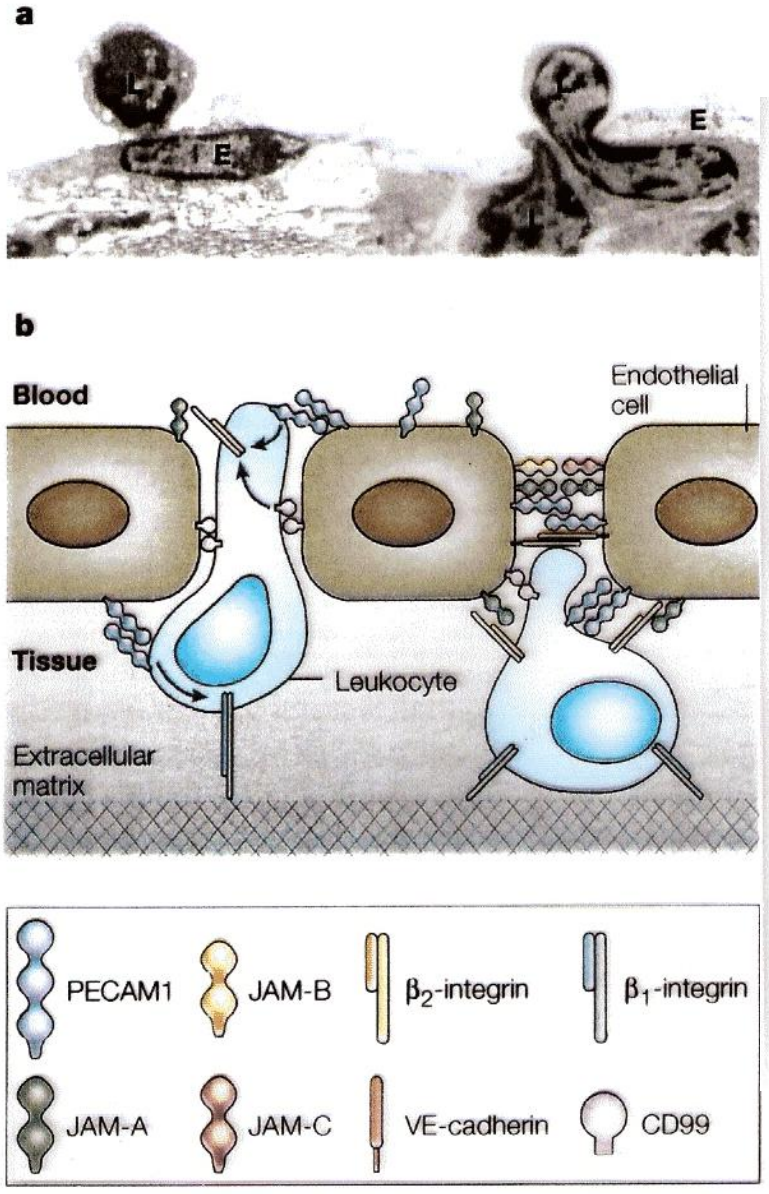


Figure 3 | **Extravasation of leukocytes from a blood vessel into lymph-node tissue. a** | An electron micrograph that shows leukocytes (L) during emigration from the lumen of a blood vessel (E). One leukocyte (left) adheres to the luminal surface of the endothelial wall. The shape of this leukocyte is relatively round, but leukocyte polarization begins at this stage. Two other leukocytes have a polarized and distorted shape, and they open the vascular junctions by breaching the endothelial layer to gain access to the lymph node. **b** | A schematic representation of the remodelling of interendothelial adhesion molecules during the transendothelial migration of polarized leukocytes. Platelet/endothelial cell-adhesion molecule 1 (PECAM1) molecules form interactions between migrating leukocytes and endothelial cells. These interactions activate the leukocyte β_1- and β_2-integrins, which then bind to endothelial ligands (such as intercellular adhesion molecules (ICAMs), vascular cell-adhesion molecule 1 (VCAM1) or junctional adhesion molecules, JAMs) and to the extracellular matrix, when the leukocyte reaches the basement membrane. The junctions between endothelial cells reseal through the engagement of vascular endothelial cadherin (VE-cadherin), JAMs and PECAM1 that are expressed on adjacent endothelial cells.

POTENCIALES PARES DE MOLÉCULAS DE ADHESIÓN

Leukocyte molecule	Endothelial-cell counter-receptor
PECAM-1 (CD31)	PECAM-1
CD99	CD99
LFA-1(CD11a OR CD18)	JAM-A
JAM-A	JAM-A[b]
Mac-1 (CD11b or CD18)	JAM-C[c,e]
JAM-C	JAM-C[b]
VLA-4 (CD49 or CD29)	JAM-B[d,e]
Endothelial-cell molecule	**Endothelial-cell counter-receptor**
VE-cadherin	VE-cadherin
PECAM-1	PECAM-1
CD99	CD99
JAM-A	JAM-A
JAM-C	JAM-C, JAM-B
JAM-B	JAM-B, JAM-C

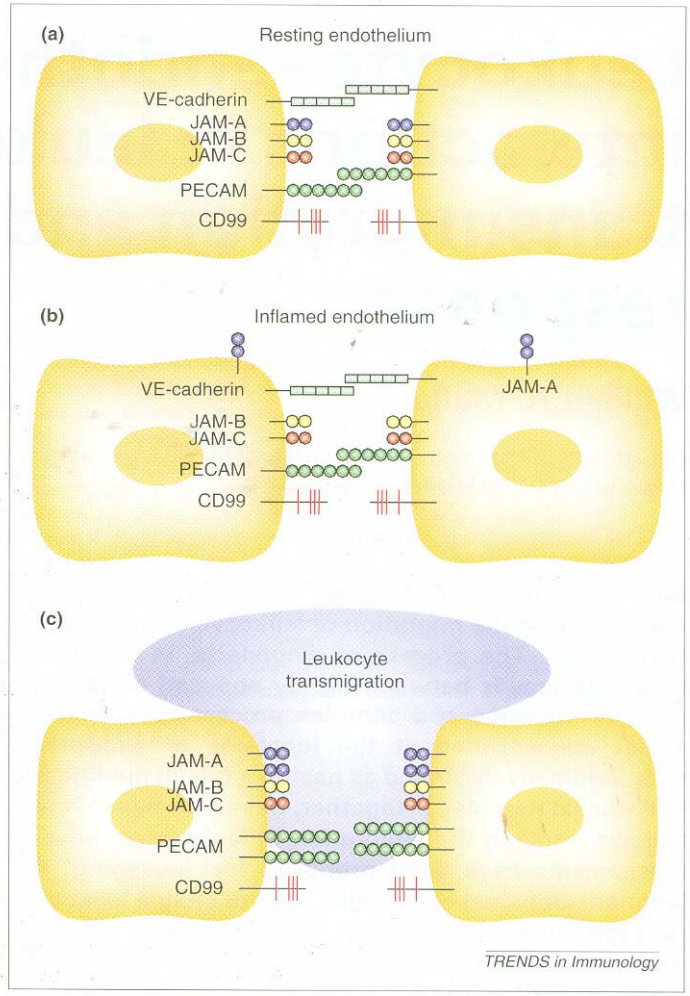
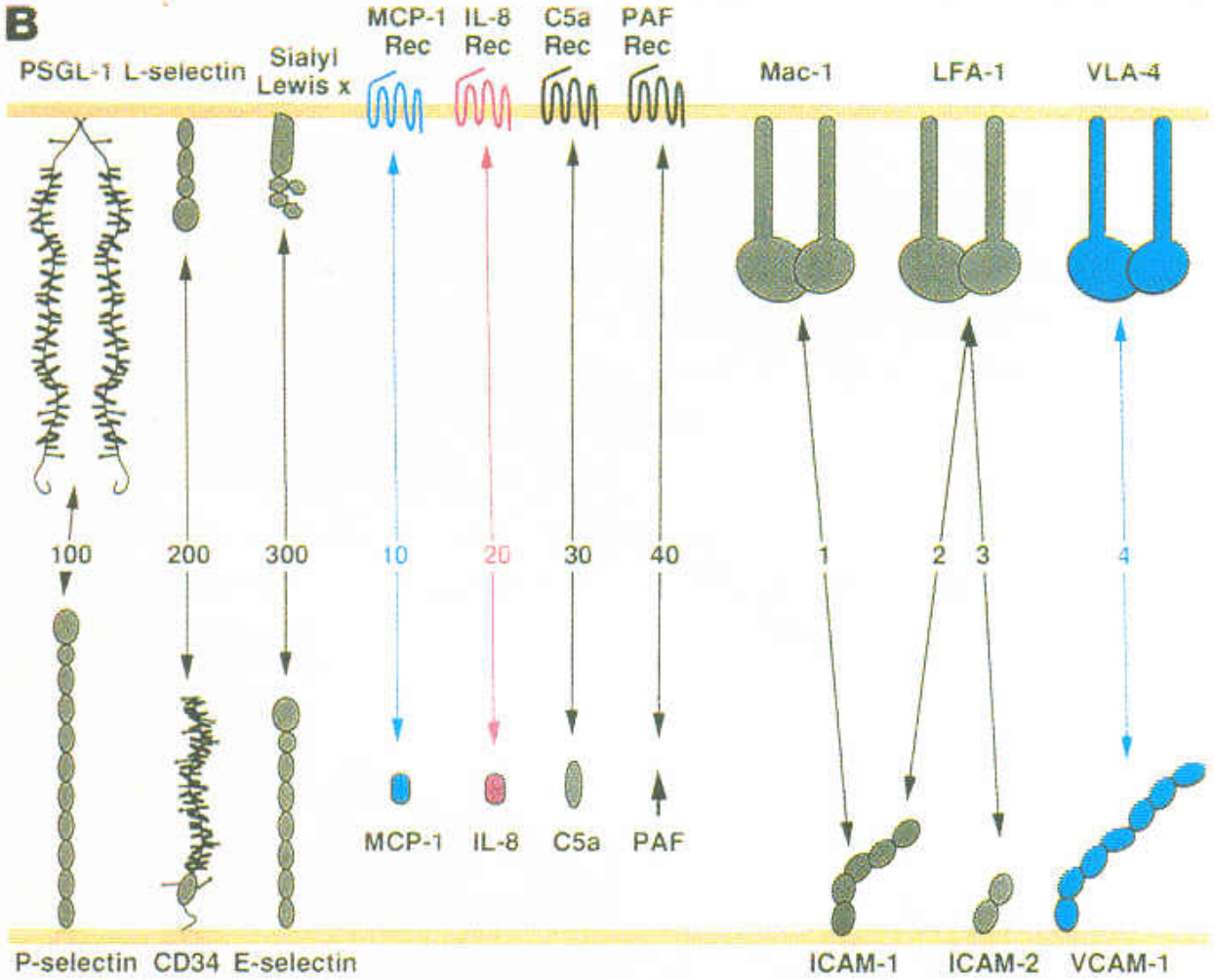


Fig. 1. Cell adhesion molecules at the endothelial-cell borders. (a) In resting endothelial cells homophilic interactions between vascular endothelial-cell specific cadherin [VE-cadherin (shown with five cadherin repeats as green rectangles)] on apposing cells, the immunoglobulin (Ig) gene superfamily molecules platelet–endothelial-cell adhesion molecule-1 [PECAM-1 (with six Ig domains indicated as circles)], junctional adhesion molecule (JAM)-A, -B and -C (with two Ig domains indicated) and CD99 (with *O*-linked sugars indicated by red 'whiskers') are established. (b) Under inflammatory conditions, there might be rearrangement of these molecules within the cell. A combination of the inflammatory cytokines tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) induces redistribution of JAM-A to the endothelial apical surface. The same combination reduces the expression of PECAM-1; IFN-γ alone (but not TNF-α or interleukin-1β) induces partial redistribution of PECAM-1 to the apical surface (not shown). (c) During leukocyte transendothelial migration, the density of VE-cadherin in the membrane adjacent to the advancing leukocyte decreases dramatically while the density of JAM-A and recycling PECAM-1 increases. It is not known whether total PECAM density increases locally or if just the density of the recycling pool increases.



Monocyte Area Codes	111, 211, 311, 112, 212, 312, 113, 213, 313, 114, 214, 314, 134, 234, 334, 144, 244, 344
Neutrophil Area Codes	121, 221, 321, 122, 222, 322, 123, 223, 323
Monocyte and Neutrophil Area Codes	131, 231, 331, 132, 232, 332, 133, 233, 333, 141, 241, 341, 142, 242, 342, 143, 243, 343
Null Area Codes	124, 224, 324

EXPRESIÓN DE VCAM EN SITIOS DE ATHEROGENESIS

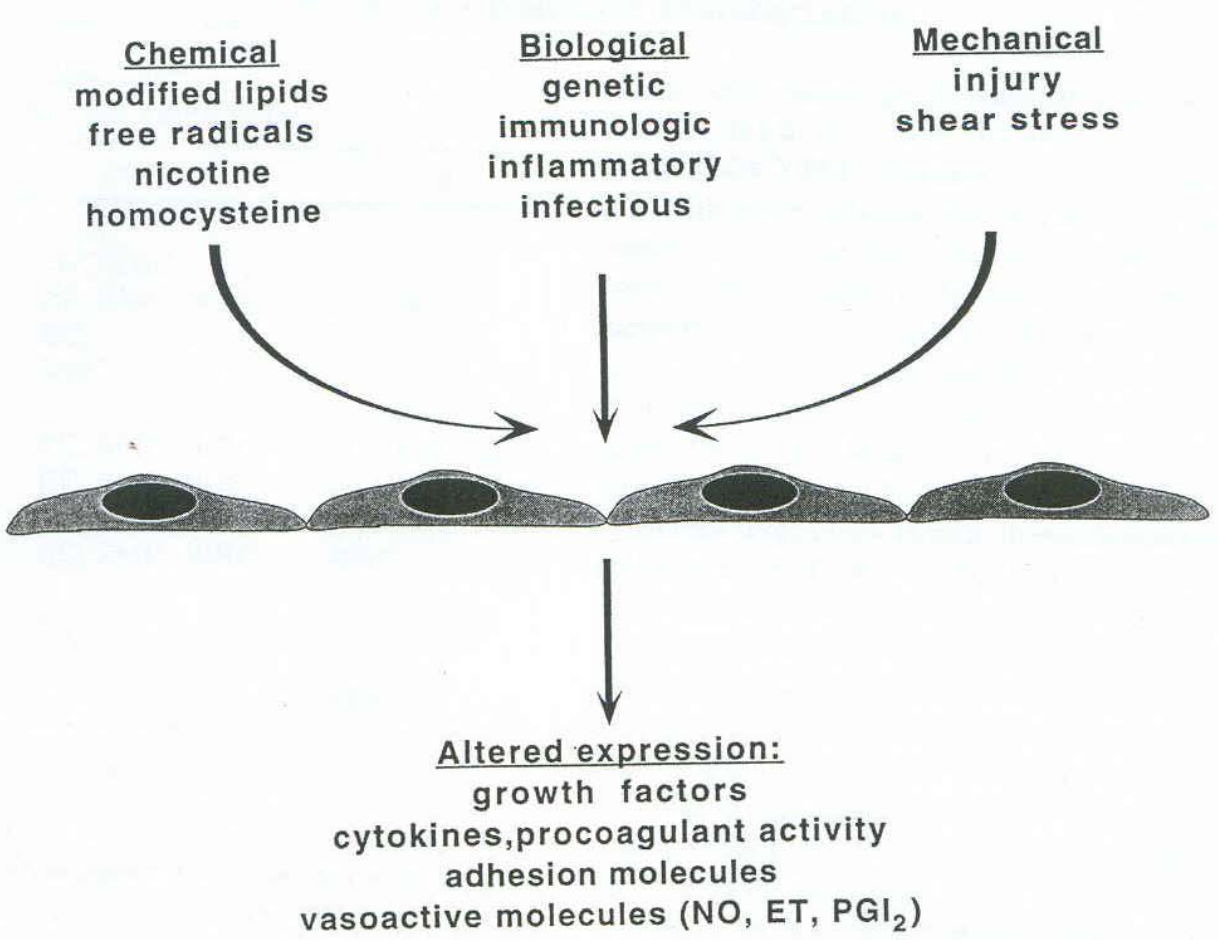


Figure 14-1 The central role of vascular endothelium. Many different stimuli may induce a similar repertoire of dysfunctional endothelial responses that ultimately contribute to clinical atherosclerosis. The endothelium provides a potential pathophysiologic link between well-established clinical risks factors such as hypercholesterolemia, cigaret smoking, hypertension, and atherogenesis. The role of the endothelial effects of other agents such as homocysteine or viral infection, as well as inflammatory cascades, remains more controversial.

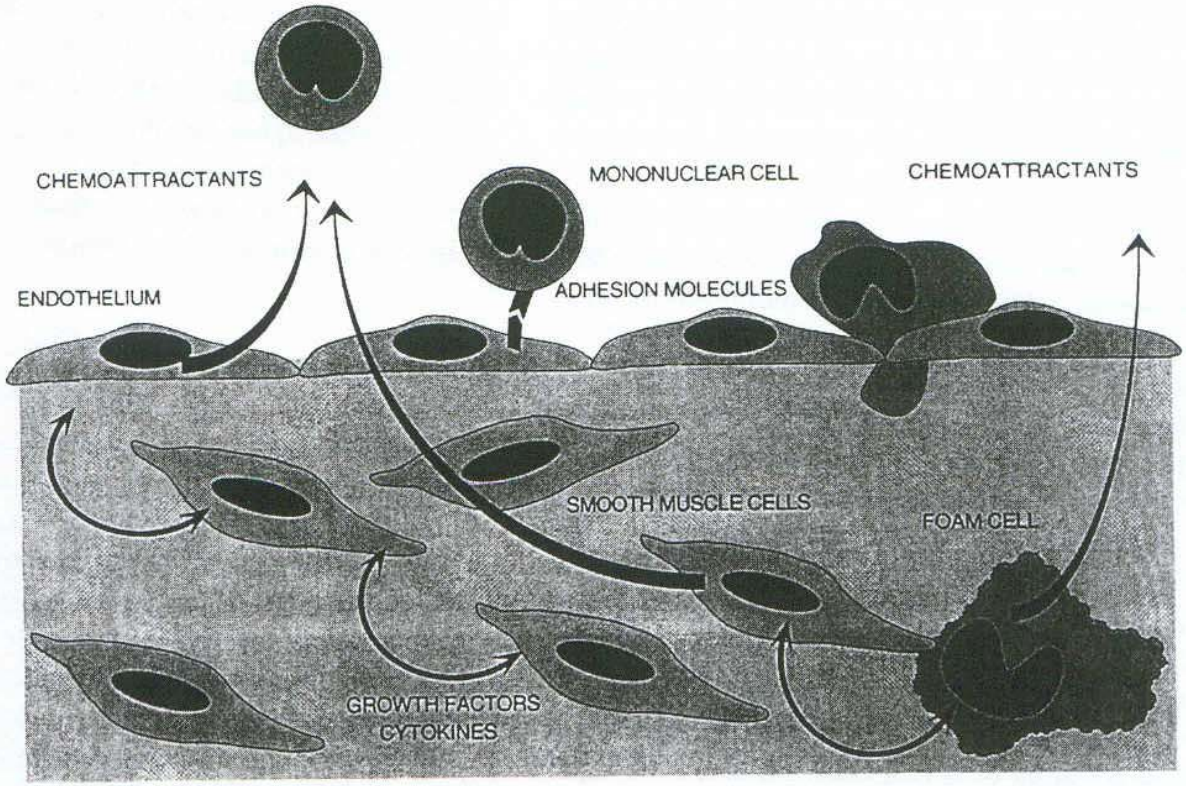
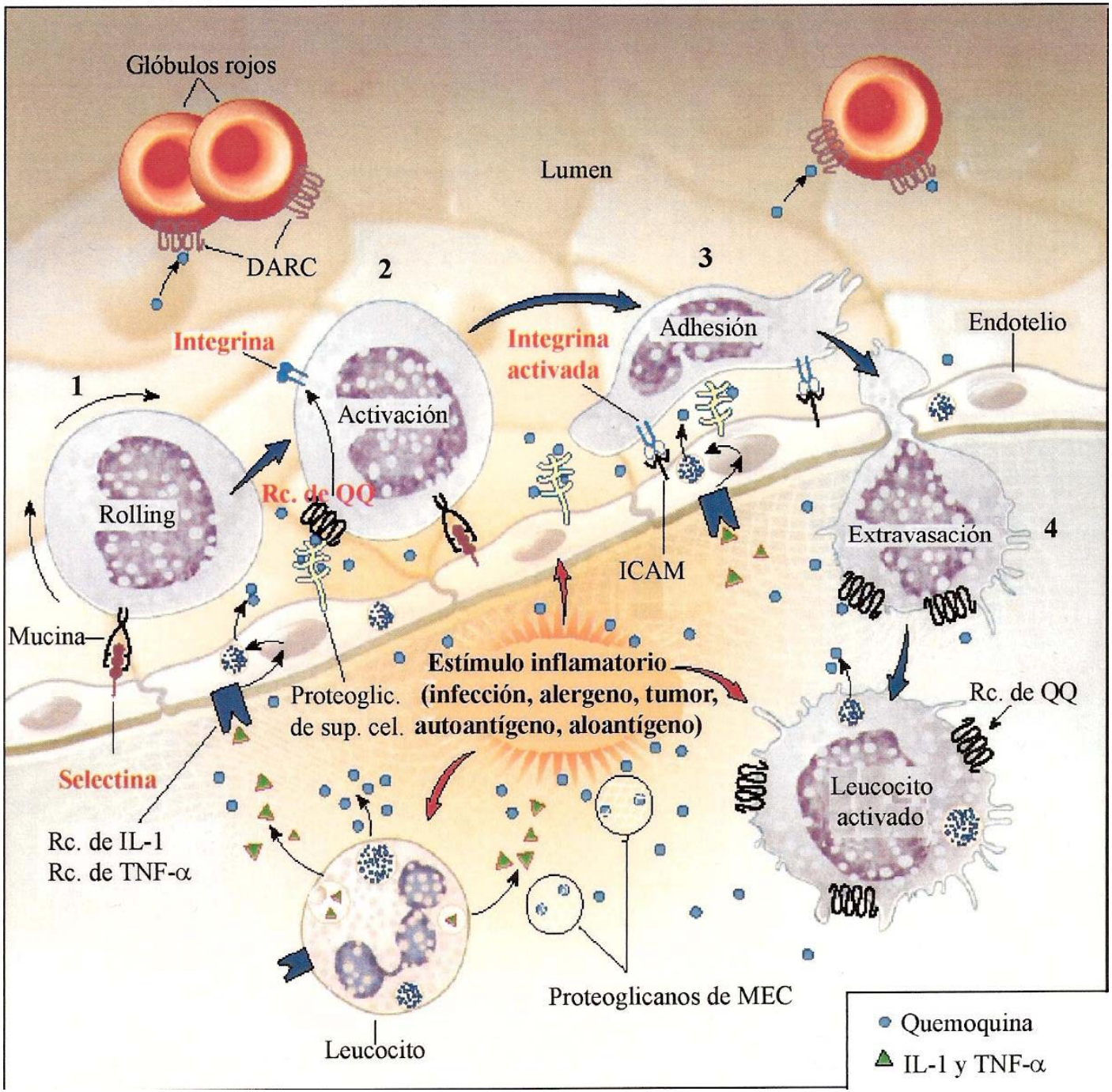


Figure 14-2 Leukocyte interactions with the vessel wall. An activated or dysfunctional endothelium may initiate a cascade of events that augment atherogenesis. These events include the recruitment of leukocytes through endothelial expression of cytokines and adhesion molecules, as well as alterations in smooth muscle cell function mediated by growth factors, cytokines, and vasoactive substances (indicated by arrows). Mononuclear cells and the foam cells they give rise to, as well as vascular smooth muscle cells, can also release growth factors and cytokines, further perpetuating this cycle.

Plate 4 (Fig. 3; *see* full caption on p. 138 and discussion in Chapter 14).

CITOQUINAS


Glóbulos rojos
DARC
Lumen
2
3
Integrina
Integrina activada
Adhesión
Endotelio
1
Activación
Rolling
Rc. de QQ
ICAM
Extravasación
4
Mucina
Estímulo inflamatorio (infección, alergeno, tumor, autoantígeno, aloantígeno)
Proteoglic. de sup. cel.
Rc. de QQ
Selectina
Leucocito activado
Rc. de IL-1
Rc. de TNF-α
Proteoglicanos de MEC
Leucocito
Quemoquina
IL-1 y TNF-α

Polipeptidos ó Glicoproteínas de bajo peso molecular

Su producción constitutiva es baja

Su producción es un evento transitorio

Se unen a receptores de alta afinidad

Su síntesis ocurre en cascadas

A basic model for cytokine action

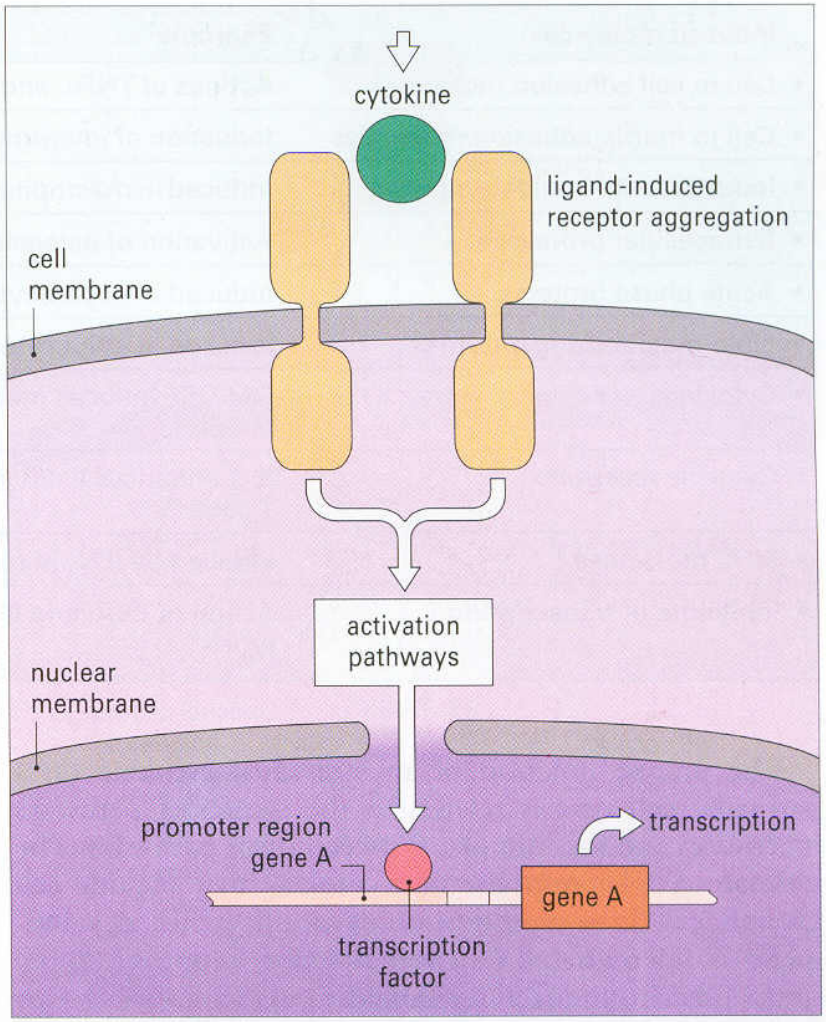


Fig. 7.8 A simple model for cytokine activation of a cell is shown. Cytokine binds to its receptor on the cells and induces dimerization or polymerization of receptor polypeptides at the cell surface. This causes activation of intracellular signalling pathways (e.g. kinase cascades), resulting in the production of active transcription factors which migrate to the nucleus and bind to the promotor or enhancer regions of genes induced by that cytokine.

CITOQUINAS

Producida por mas de un tipo de células

Poseen distintas acciones solapadas

Poseen múltiples células blanco y múltiples acciones

Radio pequeño de acción (autócrina o paracrina)

HORMONAS

Secretada por un tipo de célula especializada

Cada hormona tiene una única acción

Especificidad celular restringida a un blanco

Actúan a distancia (endocrina)

Mediadores y reguladores de la inmunidad innata

Tumor necrosis factor 17 kD macrofagos, célulasT

Interleukin-1 17kD macrofagos, celulas epiteliales y endoteliales

Interleukin-6 26kD macrofagos, células endoteliales, células T

Interleuquin 10 20 kD macrófagos

Interleuquin 12 35kD, 40 kD macrófagos, células dendríticas

Interleuquin 15 13 kD macrófagos

Interferón tipo I 18 kD α macrófagos β fibroblastos

Quimioquinas 8-10 kD macrófagos, células endoteliales,fibroblastos, células T, plaquetas

Tumor Necrosis Factor (TNF)

Fuente: macrófagos activados

Células “Target”: neutrofilos, endoteliales,macrófagos
hipotalamo, hígado, músculo

Efecto primario: activación (inflamación)
fiebre (síntesis incrementada de prostaglandinas), activa el sistema de coagulación, aumento de proteínas de fase aguda (proteìna C reactiva, α2 macroglobulina, fibrinógeno, proteína serica amiloide A), alteraciones metabólicas(músculo y lípidos)

Intracellular signalling pathways induced by TNF

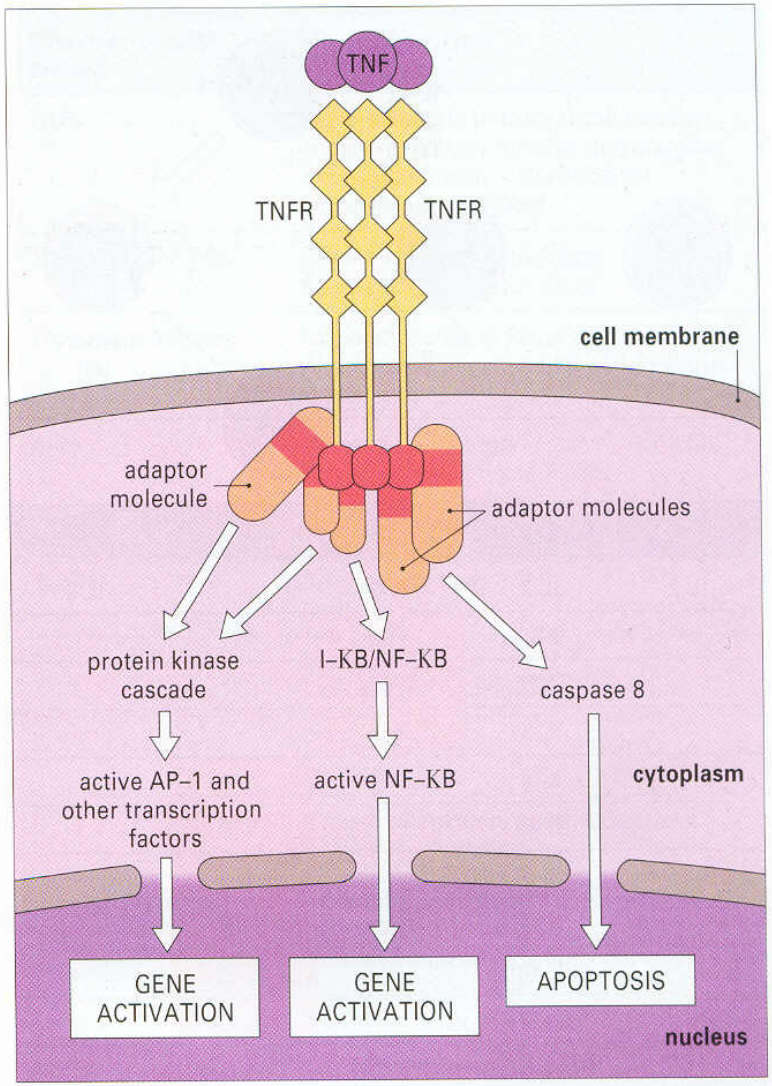


Fig. 7.11 TNF induces the trimerization of the TNF receptor on the cell surface, which causes adaptor molecules to be recruited to the receptor complex. One pathway leads to the activation of caspase-8 and apoptosis. Other pathways lead to the activation of the transcription factors AP-1 and NFκB, which cause gene activation and may offset the effects of the caspase pathway.

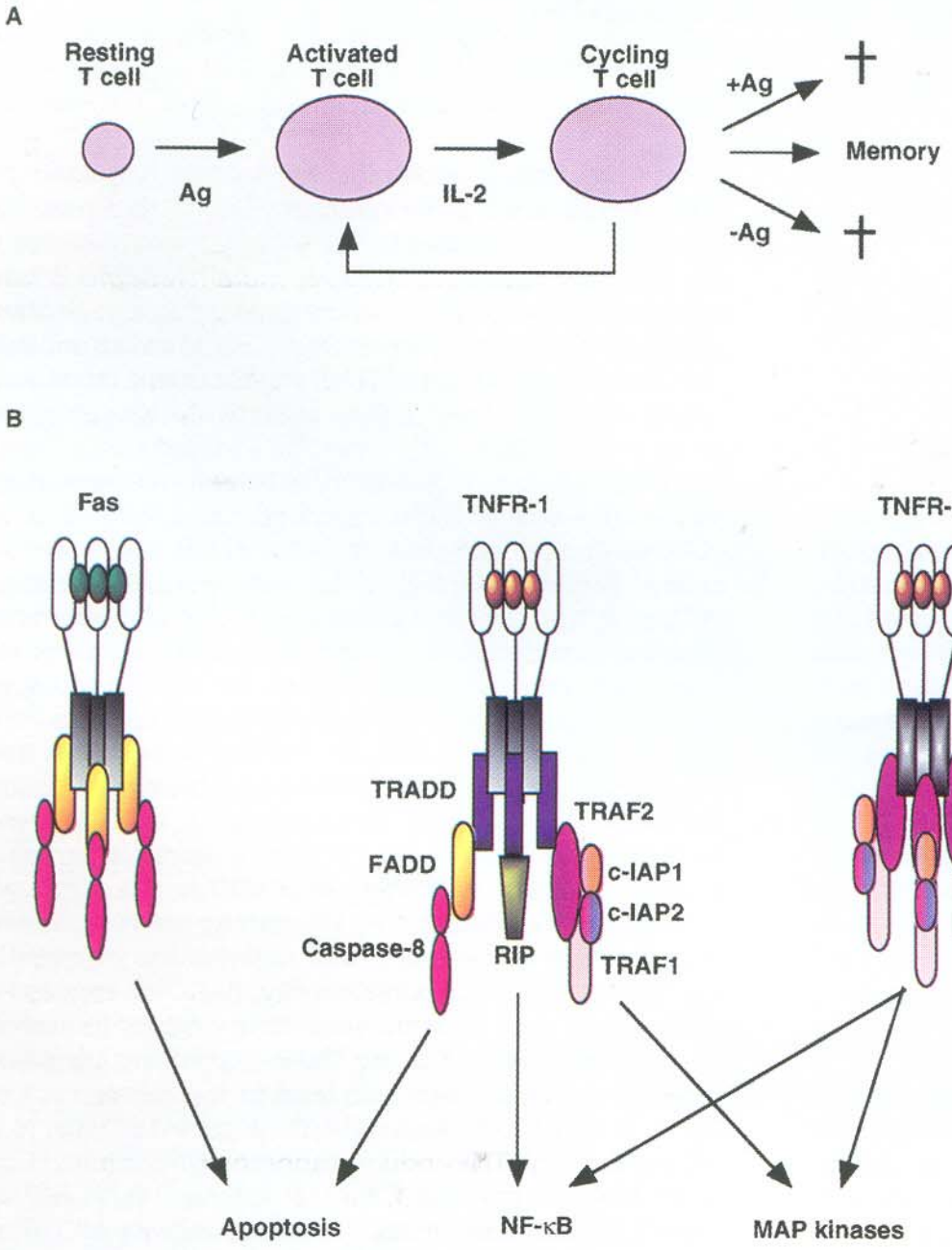


Figure 1. TNFR Signaling and T Cell Homeostasis

(A) Propriocidal and lymphokine-withdrawal death in T cell homeostasis. Antigen (Ag)-activated T cells are driven into cell cycle by cytokines like IL-2. Restimulation of the same T cells by antigen leads to propriocidal apoptosis mediated by death cytokines. Removal of antigen stimulation results in death receptor-independent, lymphokine withdrawal death. (B) Proximal components of the Fas, TNFR-1, and TNFR-2 signal transduction pathways.

Interleukin-1 (IL-1)

Fuente: macrófagos activados, epiteliales, endoteliales

Células target: endoteliales, macrófagos

Hipotálamo, hígado, músculo

Efecto primario: activación (inflamación)

Fiebre (síntesis incrementada de prostaglandinas), activa el sistema de coagulación,aumento de proteínas de fase aguda (proteína C reactiva, $\alpha 2$ macroglobulina, fibrinógeno, proteína sérica amiloideA), alteraciones metabólicas (músculo y lípidos)

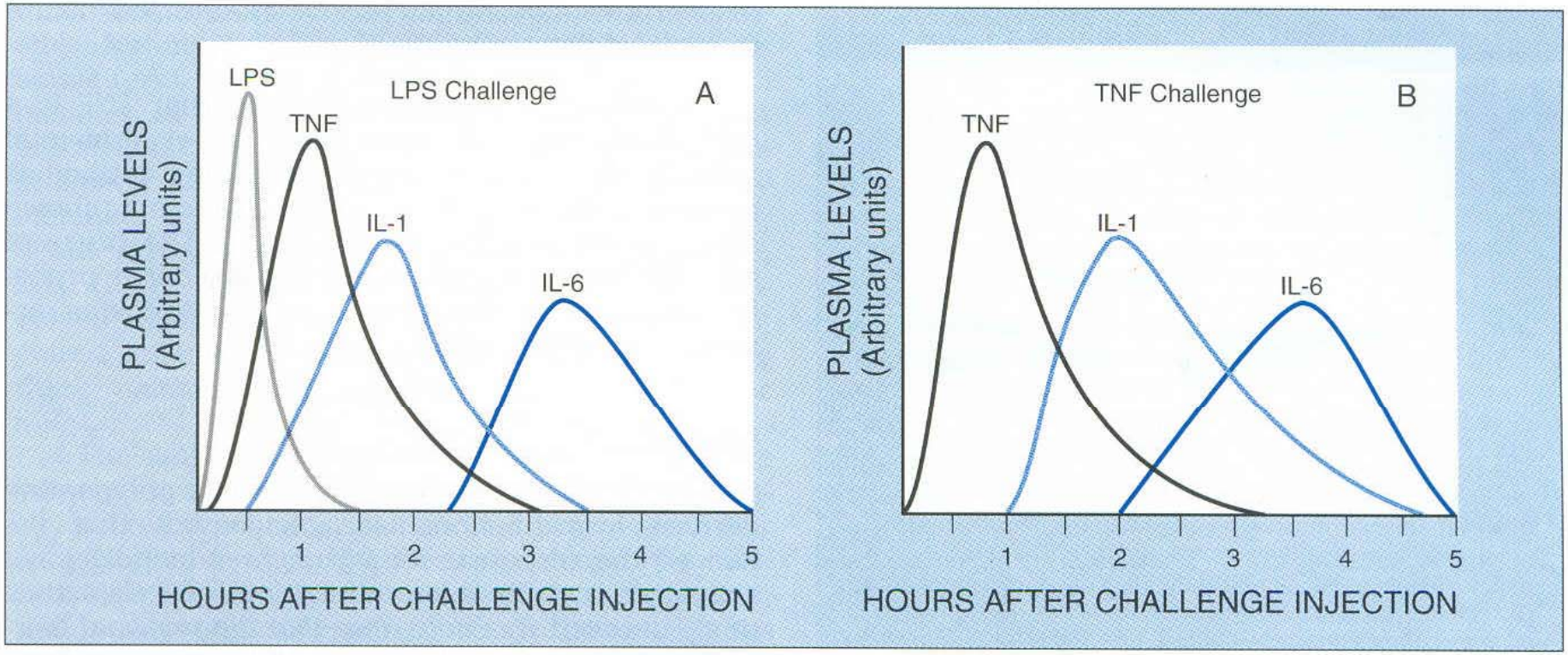
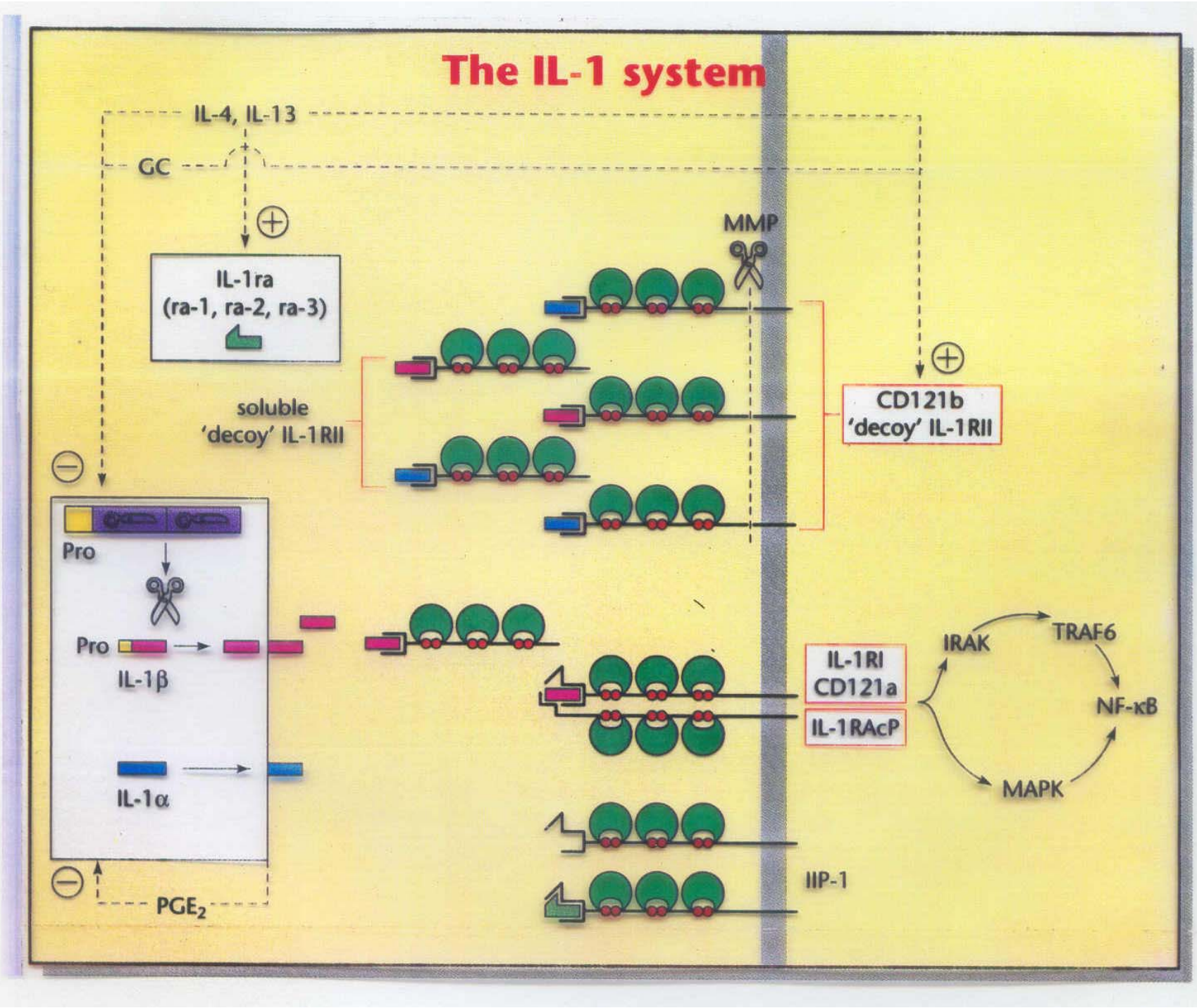


FIGURE 12–3. Cytokine cascades in sepsis. Following injection of LPS *(A)*, there are successive waves of TNF, IL-1, and IL-6 detectable in plasma. Injection of TNF *(B)* produces successive waves of IL-1 and IL-6. In the presence of antibody to TNF, LPS-induced plasma elevations of IL-1 and IL-6 are inhibited; and in the presence of antibody to IL-1, plasma elevations of IL-6 are inhibited. These data suggest that there are ordered cascades of cytokine production: LPS induces TNF, which induces IL-1, which induces IL-6 synthesis.


The IL-1 system
IL-4, IL-13
GC
IL-1ra
(ra-1, ra-2, ra-3)
MMP
soluble
'decoy' IL-1RII
CD121b
'decoy' IL-1RII
Pro
Pro
IL-1β
IL-1α
PGE2
IL-1RI
CD121a
IL-1RAcP
IRAK
TRAF6
NF-κB
MAPK
IIP-1

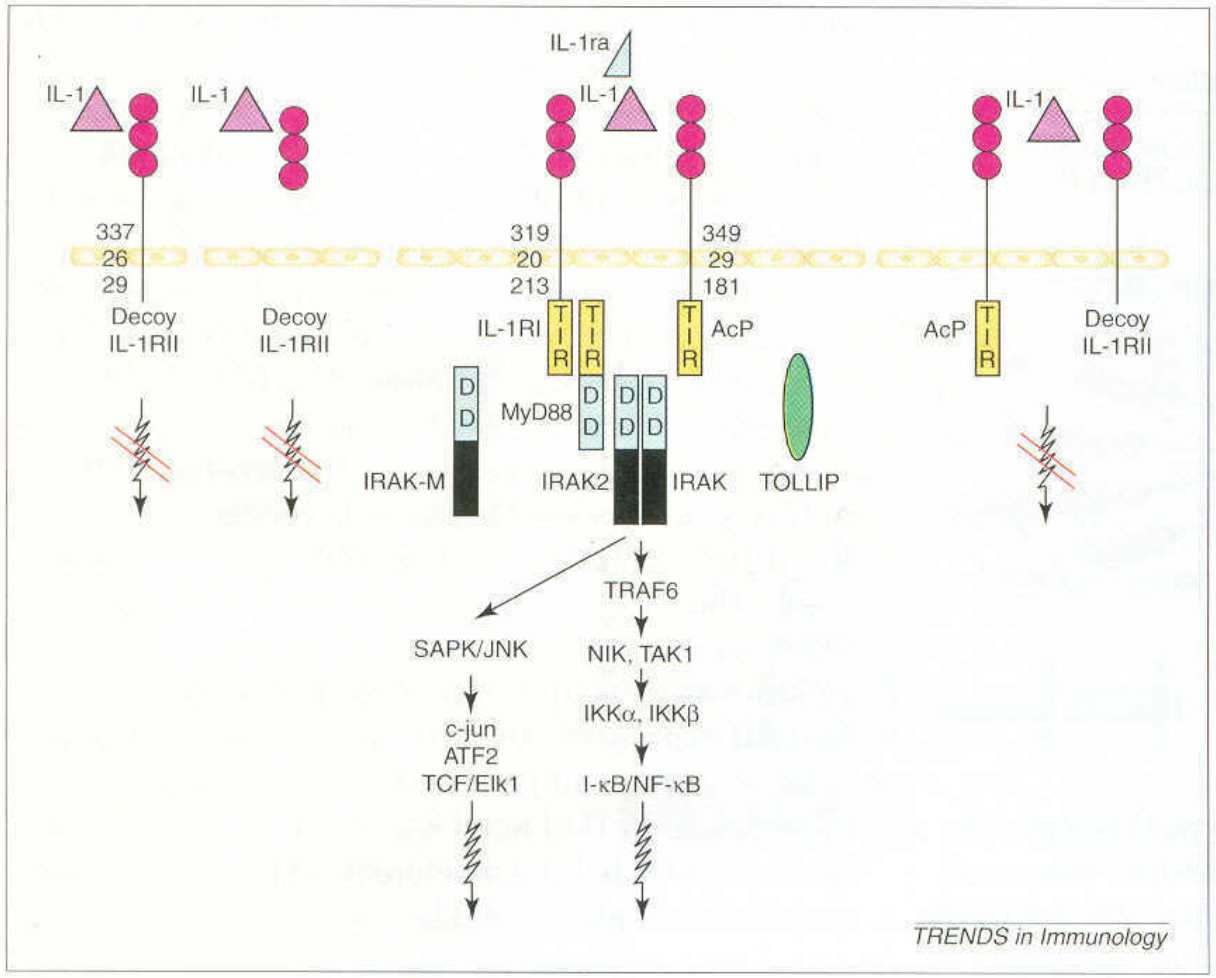


Fig. 1. The type II interleukin-1 receptor (IL-1RII) as a decoy. The signaling IL-1R complex [IL-1RI and accessory protein (AcP)] activates the MyD88 cascade, leading to activation of NF-κB and AP-1. The cascade consists of adapter proteins (MyD88 and TRAF6), kinases (IRAKS, IKK and JNK) and a shuttle molecule (Tollip for IRAK). In membrane-bound or released form, IL-1RII captures IL-1 and prevents it from forming a signaling receptor complex. In addition, it forms a dominant negative nonsignaling complex with the AcP. Abbreviations: ATF-2, activating transcription factor 2; DD, death domain; IL-ra, IL-1R antagonist; IKK, inhibitor of nuclear factor κB kinase; IRAK, IL-1R-associated kinase; JNK, Jun N-terminal kinase; NF, nuclear factor; NIK, nuclear factor κB-inducing kinase; SAPK, stress-activated protein kinase; TAK, transforming growth factor β-activated kinase; TCF, T-cell factor; TIR, Toll/IL-1R domain; TRAF, tumor necrosis factor receptor associated factor. Pink circles represent Ig domains. Numbers refer to the amino acids per domain.

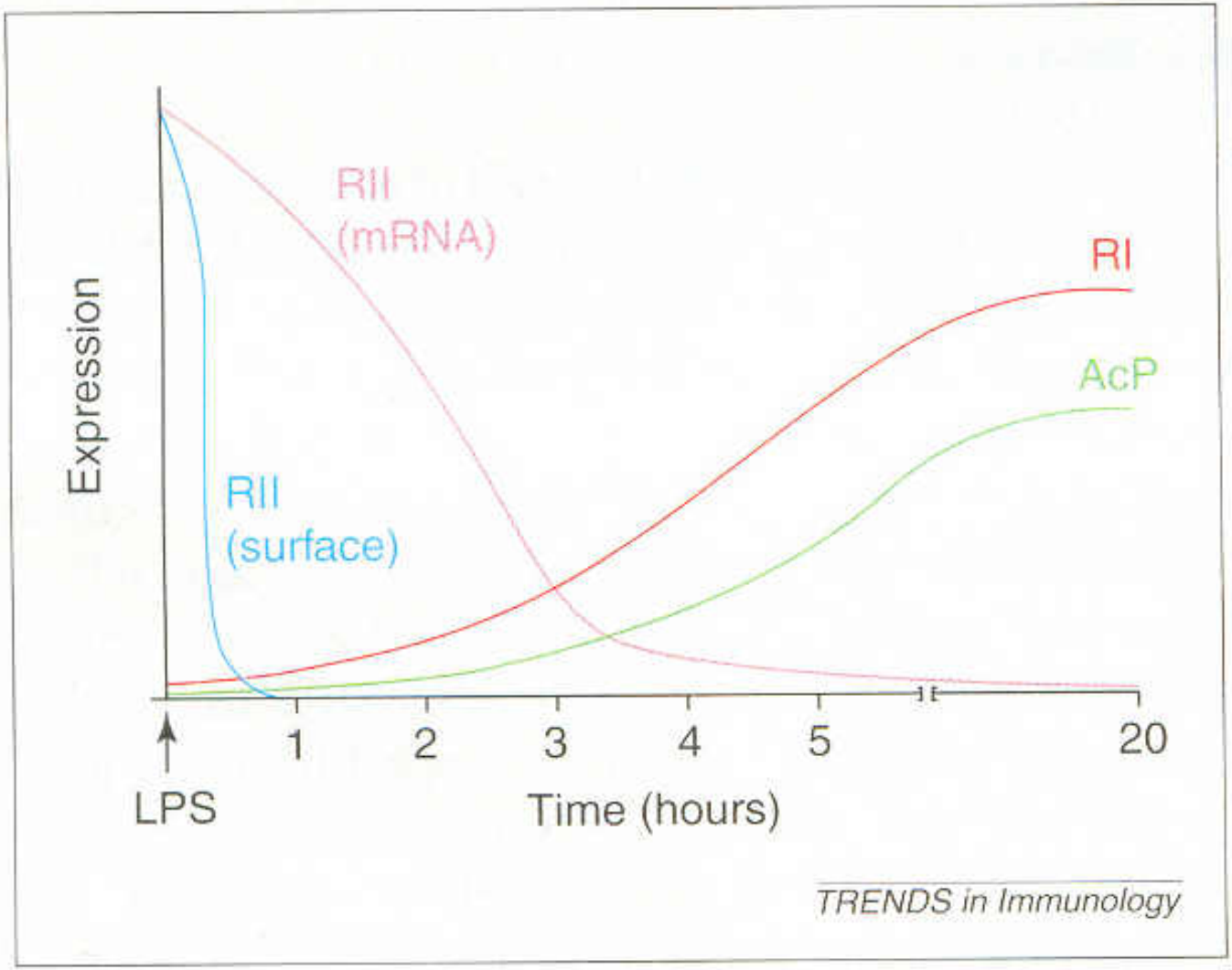


Fig. 3. Effect of lipopolysaccharide (LPS) on interleukin-1 type II receptor (IL-1RII), IL-1RI and IL-1R accessory protein (AcP) expression. LPS causes rapid shedding of the decoy IL-1RII, followed by inhibition of mRNA transcript expression. Concomitantly, the expression of IL-1RI and IL-1 AcP is induced.

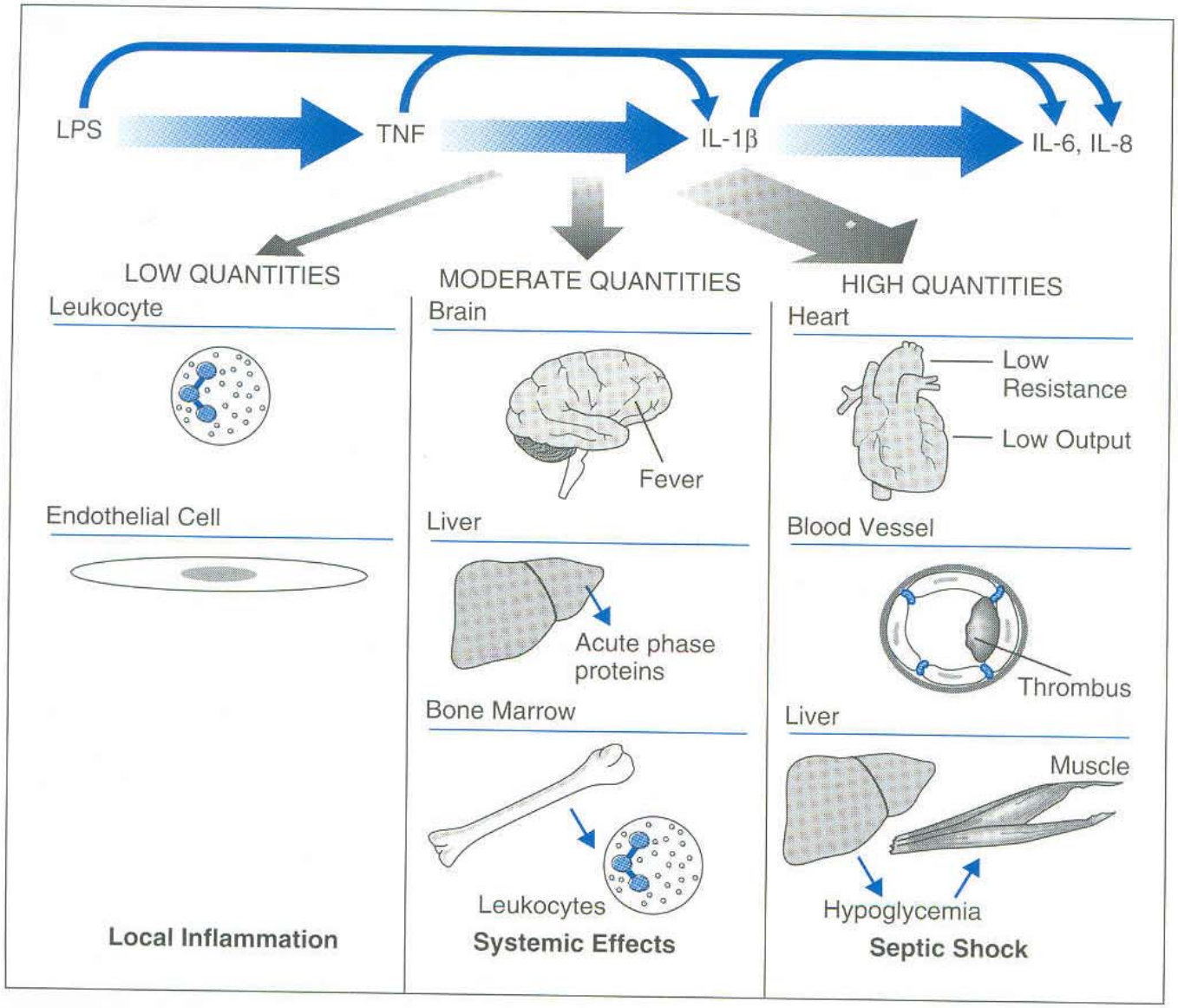


FIGURE 12–2. The LPS-induced cytokine cascade. Bacteria LPS acts on macrophages to release tumor necrosis factor (TNF). TNF induces macrophages to release interleukin-1β (IL-1β). IL-1β acts on macrophages and vascular endothelial cells to release IL-6 and IL-8. (The thinner arrows indicate that LPS directly induces IL-1β, IL-6, and IL-8 and that TNF directly induces IL-6 and IL-8, but these actions are amplified through the cascade.) When low quantities of cytokines are released, the effects are local. With moderate quantities, systemic effects can be detected. At high levels, these cytokines produce the syndrome of septic shock.

TNF e IL-1

- **IL-1 no produce daño tisular por si misma, aunque puede potenciar el producido por TNF**
- **IL-1 no es letal a altas concentraciones**
- **IL-1 no causa lesiones hemorrágicas en tumores**
- **IL-1 no induce muerte por apoptosis en tumores u otras células**
- **IL-1 potencia la acción de CSF sobre las células de la médula osea**

QUÉ ES EL SISTEMA IFN?

CÓMO FUNCIONA EL IFN PARA INHIBIR
LA MULTIPLICACIÓN DE LOS VIRUS?

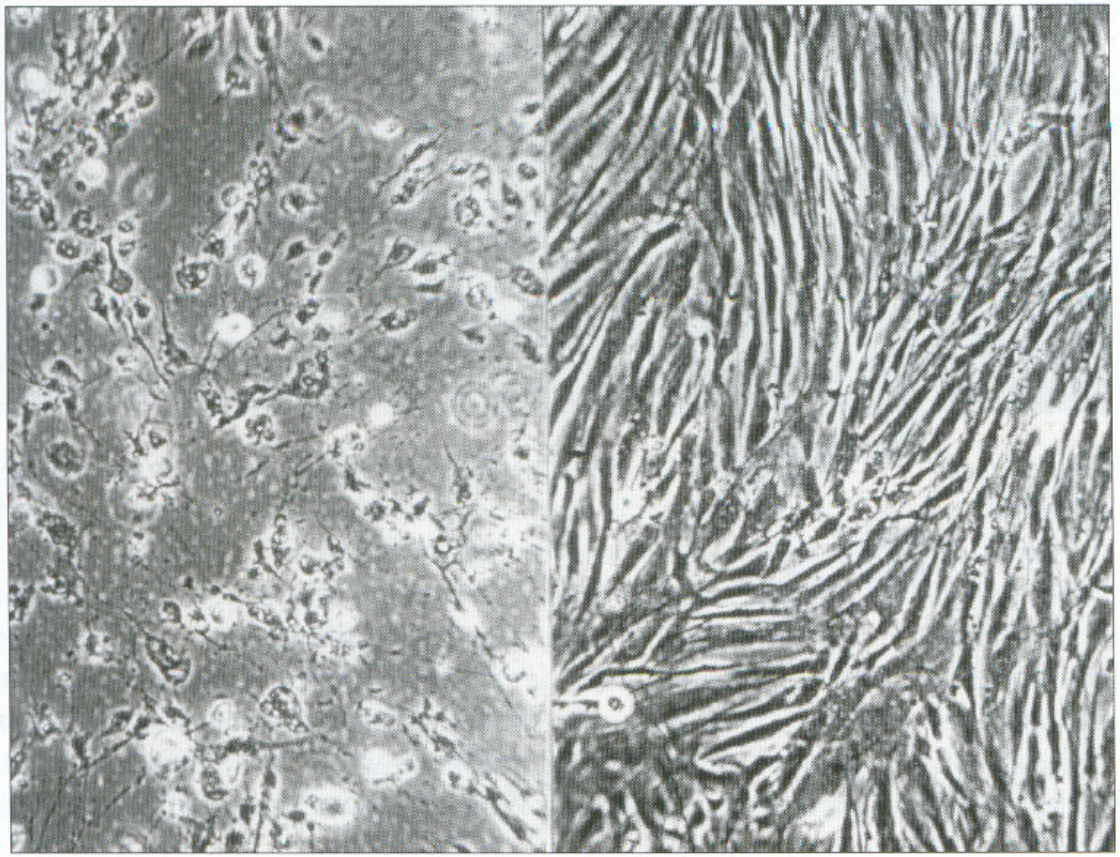
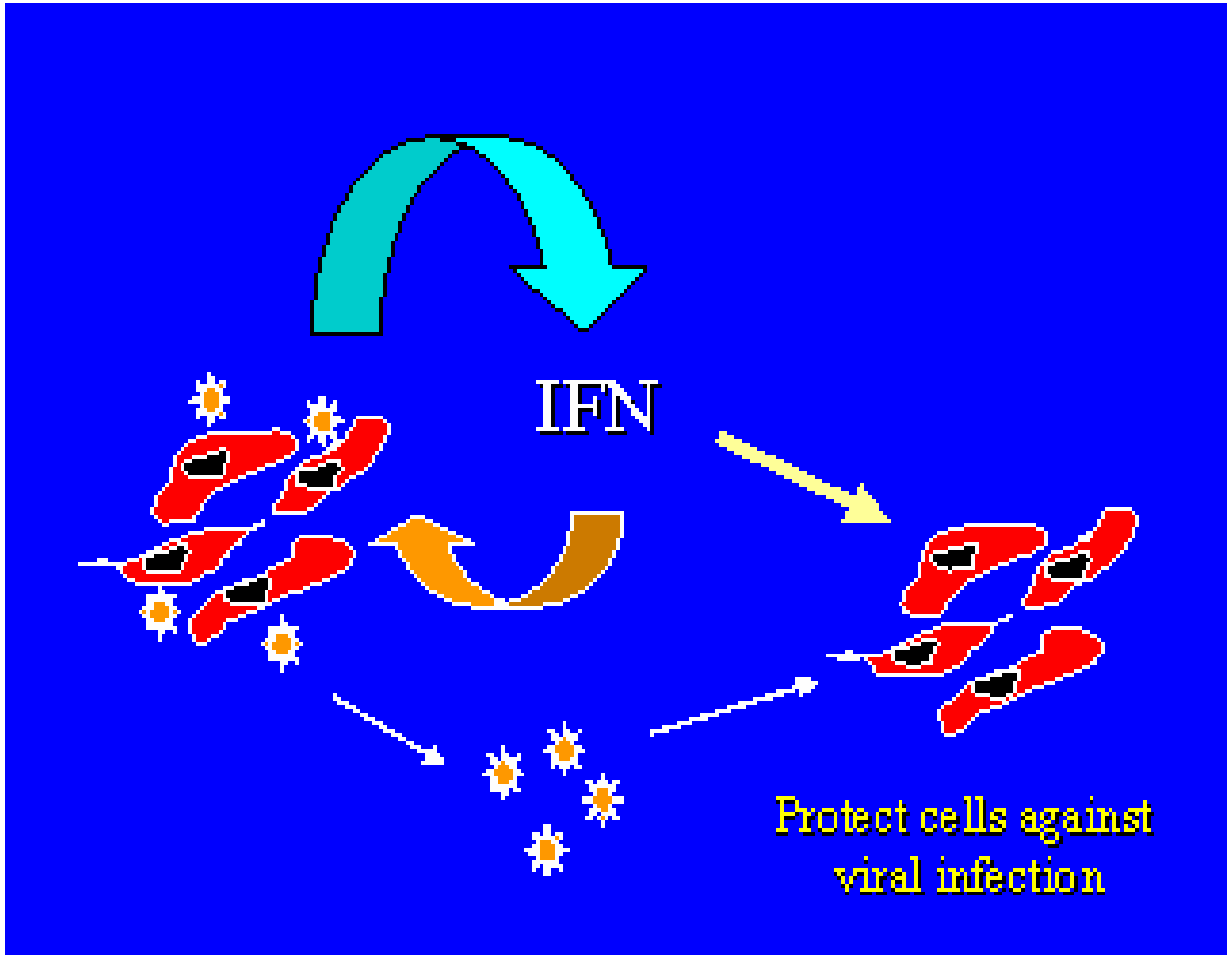
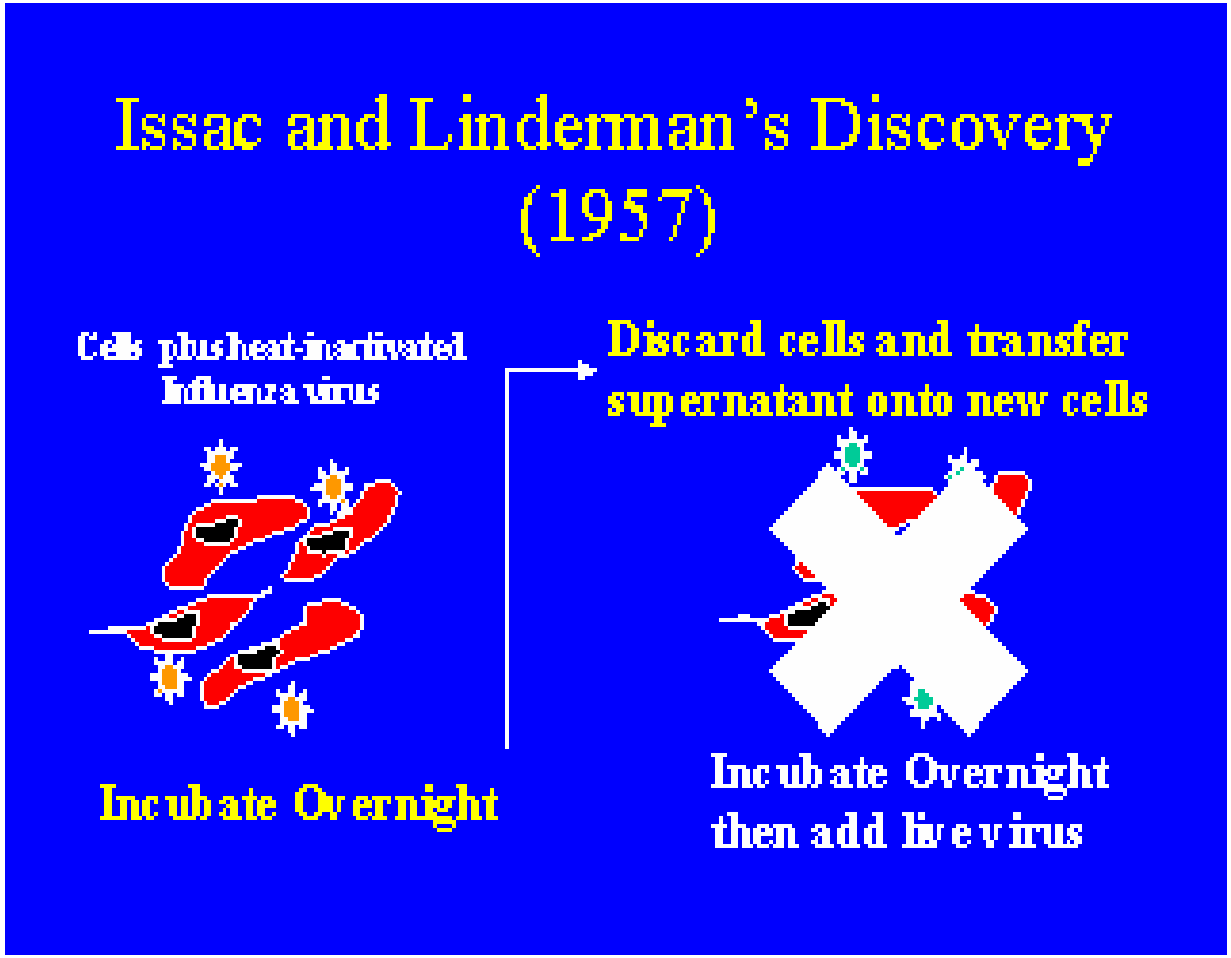


Fig. 7.1 Antiviral action of interferon. Fibroblasts in tissue culture were infected with a cytopathic virus. Cells on the right pre-treated with interferon survive while untreated cells are killed by the replicating virus.

Protección de la infección viral



Interferencia en virus



Interferon (IFN) tipo I

Fuente: macrófagos (α), Fibroblastos (β). Su síntesis es inducida por infección viral

Efecto: Inhibe la replicación viral sintetizando enzimas como 2´- 5´ oligoadenilato sintetasa que interfiere con la replicación del RNA y DNA viral.

Incrementa el potencial lítico de células NK.

Incrementa el MHC clase I aumentando la eficiencia de los CTL.

Inhibe la proliferación celular (fue usado como antiproliferativo para ciertos tumores)

Mediadores y reguladores de la inmunidad específica

Interleukin 2 14-17 kD células T

Interleukin 4 20 kD células TCD4+

Interferón –gama 21-24 kD células T, Células NK

Lymphotoxin 24kD células T

Interleukin-5 20kD células T

Interleukin-2 (IL-2)

Fuente: Células T

Células “target”: Células T, células B, células NK

Efecto: Factor de crecimiento autócrino y parácrino para linfocitos T. Estimula la síntesis de otras citoquinas derivadas de células T

Estimula el crecimiento y la activación de NK

Es un factor de crecimiento de células B, estimula la síntesis de Abs

Puede promover apoptosis de células T activadas por Ags

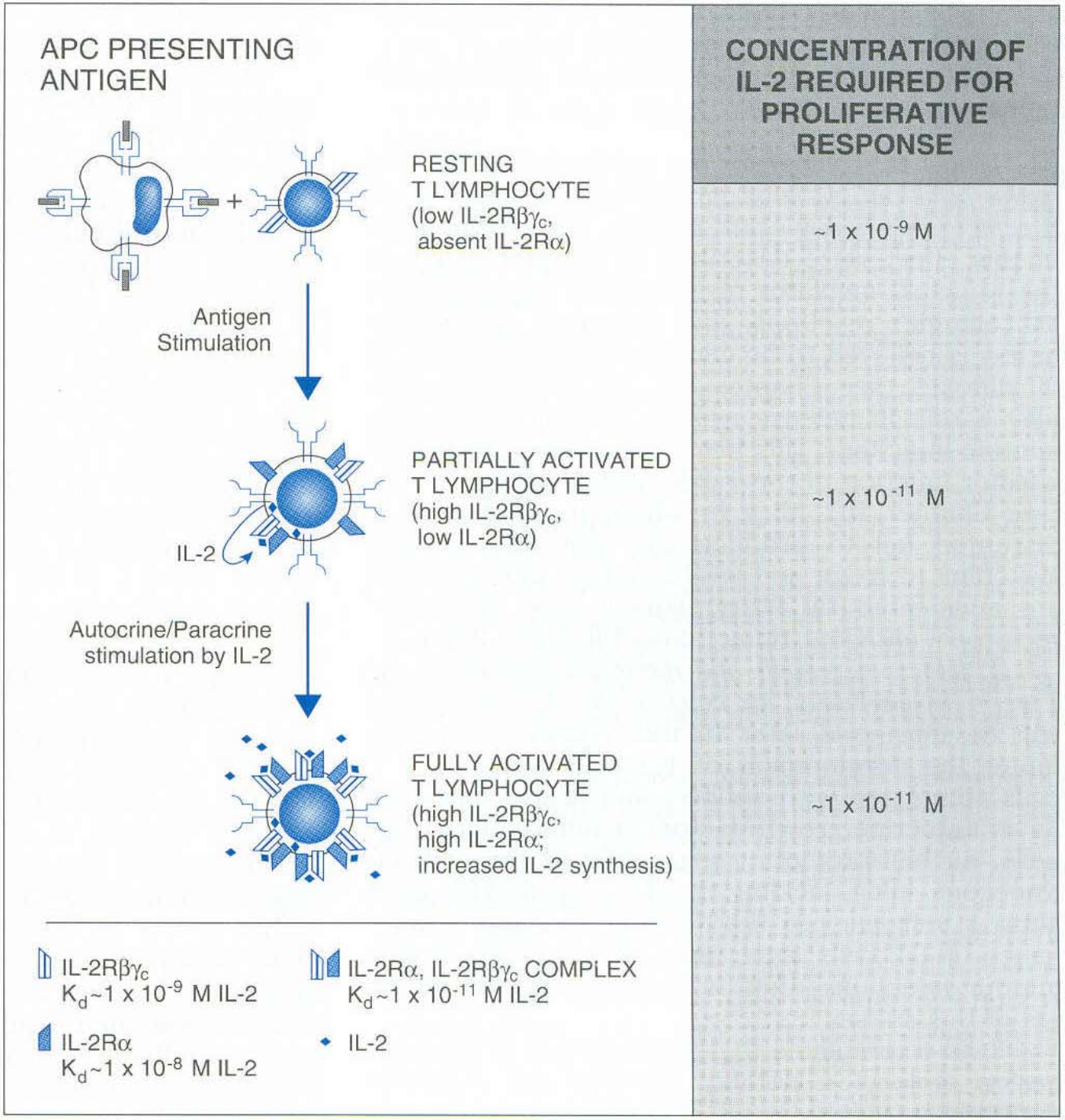


FIGURE 12–4. IL-2 receptors. The high-affinity IL-2 receptor (IL-2R) is composed of a complex of polypeptides (IL-2R$\beta\gamma_c$ and IL-2Rα) that interact to bind IL-2 with high affinity. Resting T cells express only IL-2R$\beta\gamma_c$, which binds IL-2 with lower affinity. T cell activation by antigen and an antigen-presenting cell (APC) leads to IL-2Rα synthesis and expression, thereby increasing the affinity of the IL-2R$\beta\gamma_c$ receptor and allowing growth stimulation at physiologic IL-2 concentrations. IL-2 produced by the activated T cell further increases IL-2Rα expression and stimulates IL-2 synthesis, providing a positive amplification system.

Structures of the IL-2 and IL-4 receptors

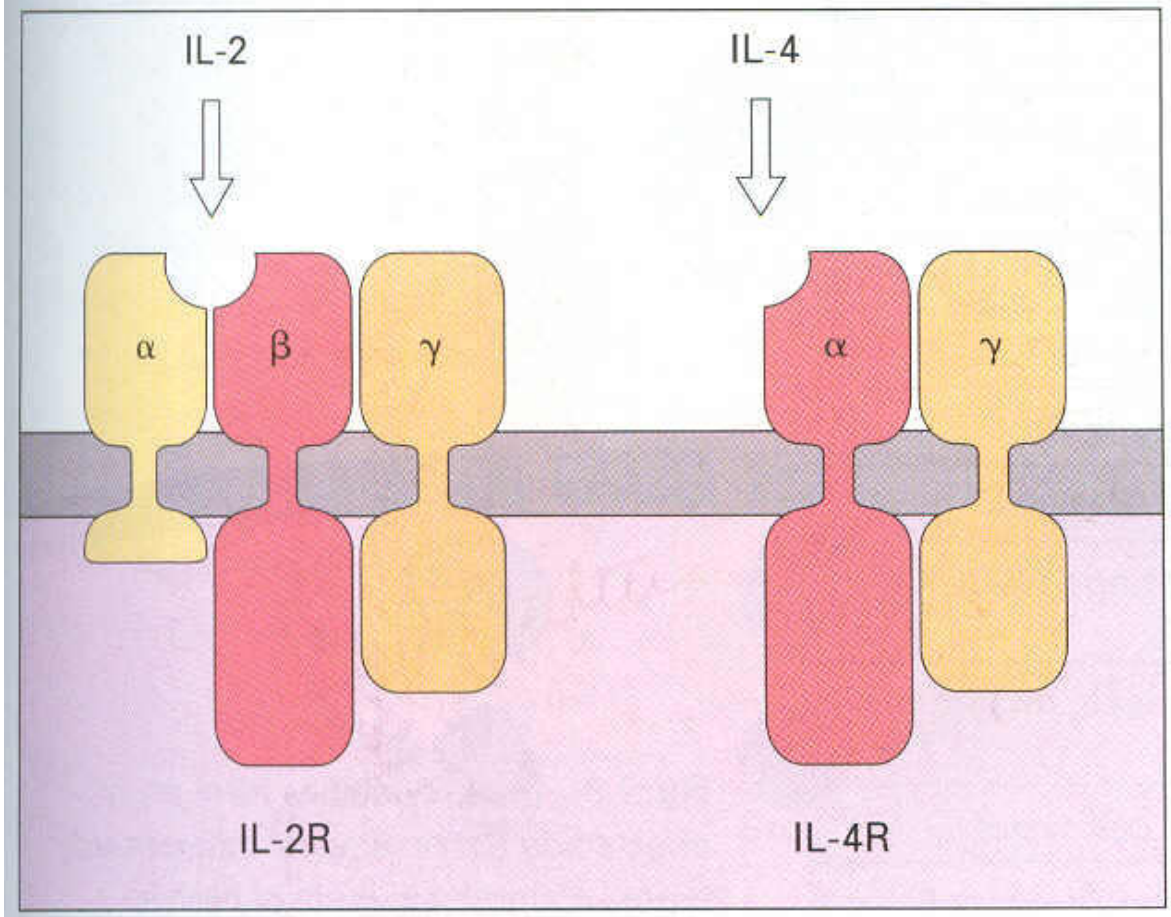


Fig. 7.7 The high-affinity IL-2 receptor is formed by three polypeptide chains, of which the α and β chains bind to the cytokine, while the γ chain is involved in signalling to the cell. The IL-4 receptor shares the γ signalling chain, but has a unique α chain which specifically recognizes IL-4.

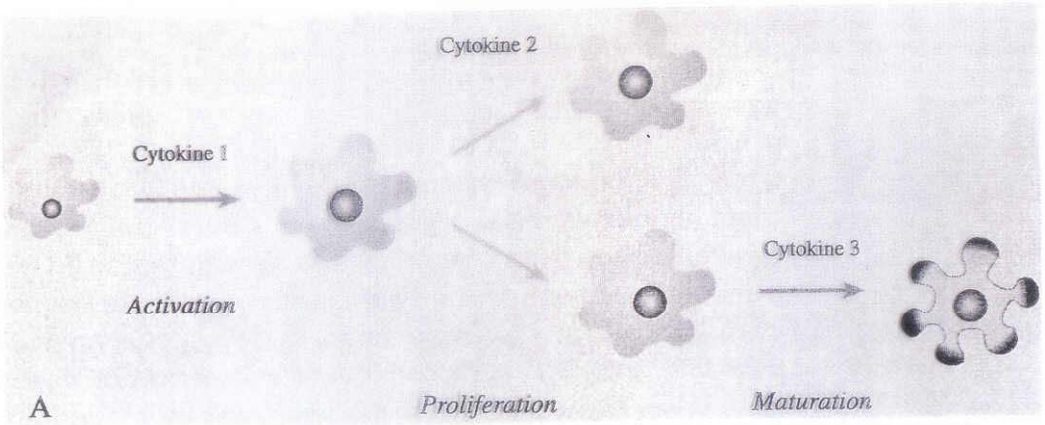
Interferon gama (IFN gama)

Fuente: células T, células NK

Células “target” : macrófagos, células endoteliales

Efecto primario: Activa macrófagos, incrementa el MHC I, promueve diferenciación de linfocitos T, activa neutrofilos, estimula la actividad citolítica de células NK, es activador de células del endotelio vascular, potencia la acción del TNF sobre células endoteliales

Cytokines, Chaos, and Complexity



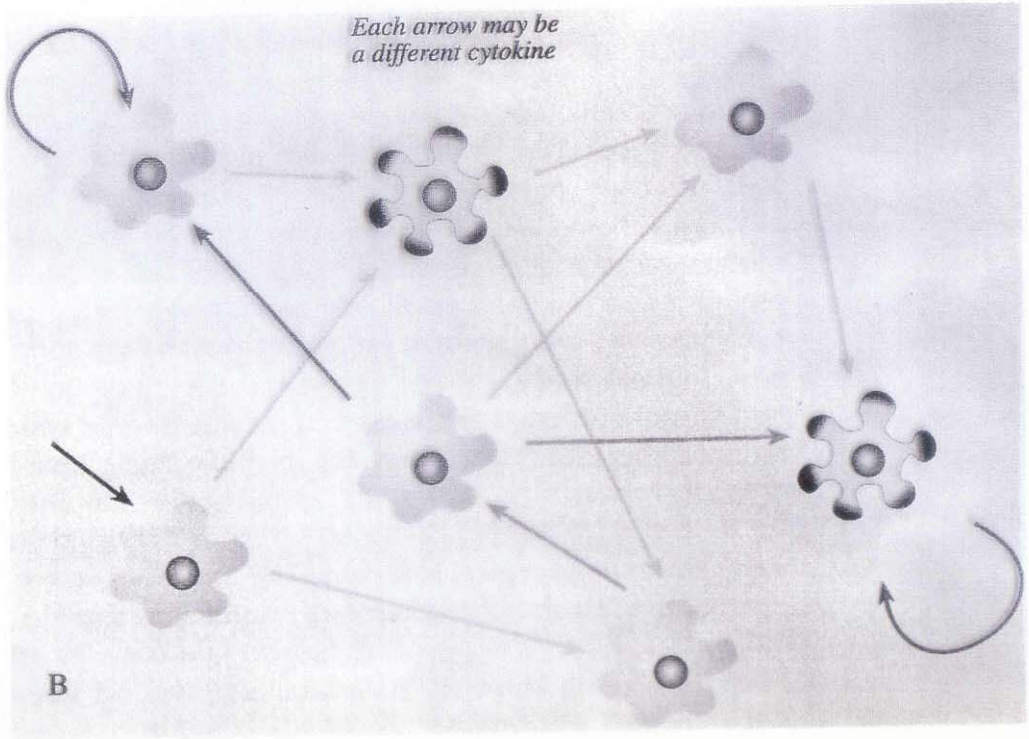


Figure 1. Linear and Network Models of Cytokine Action

Linear models of cytokine control of cellular function (A) have been replaced by network models (B) that take into account cytokine interactions.

QUIMIOQUINAS

SON PROTEINAS QUIMIOATRACTANTES QUE POSEEN UNA ACCIÓN CENTRAL EN LAS RESPUESTAS INMUNE E INFLAMATORIAS DEBIDO A LA ATRACCIÓN Y ACTIVACIÓN DE LEUCOCITOS

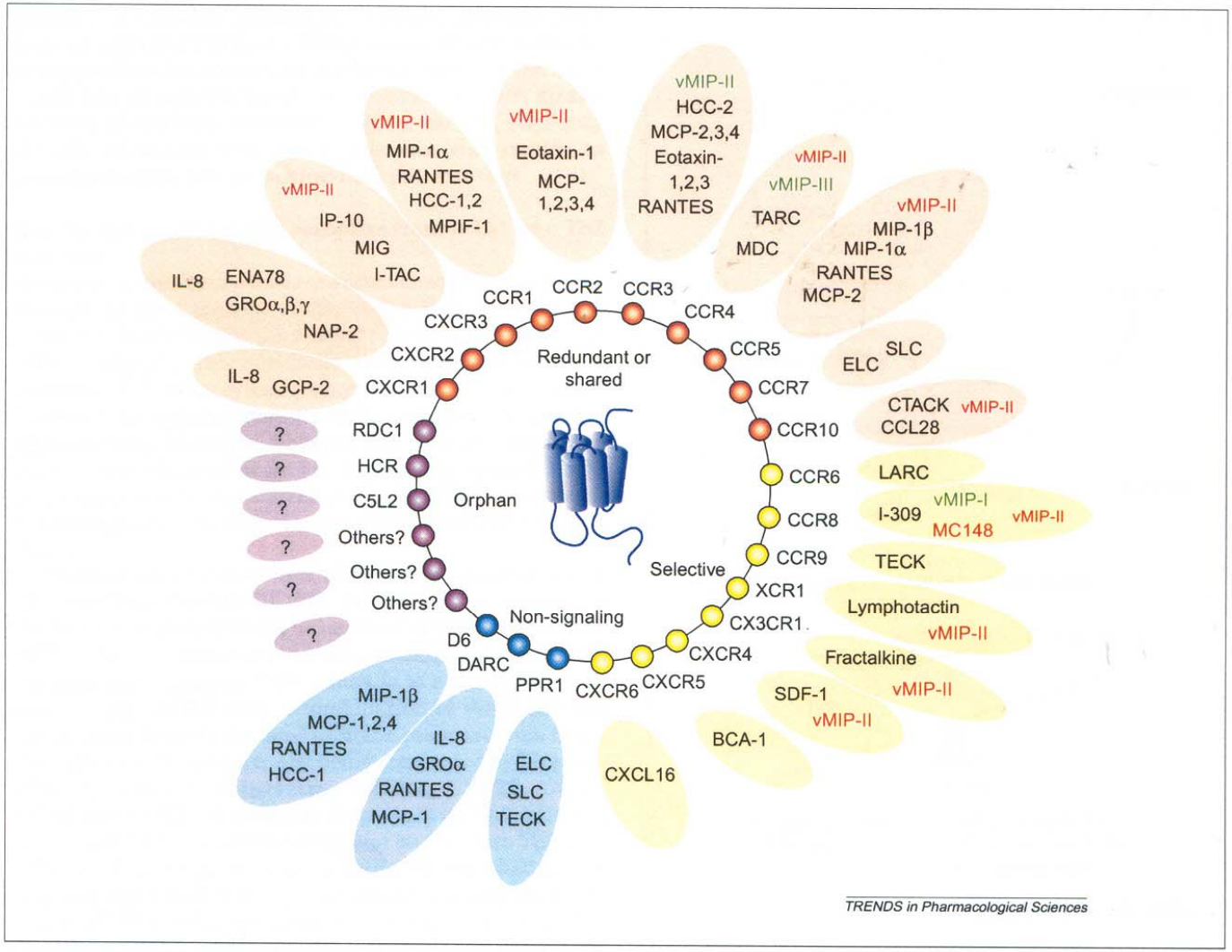


Fig. 1. The chemokine system. In the inner circle the endogenous chemokine receptors are arranged according to their general properties: (1) 'selective' – receptors with a single, well defined endogenous chemokine ligand (yellow); (2) 'redundant' or 'shared' – receptors that are controlled by more than one chemokine ligand (red); (3) 'orphan' – receptors that, structurally, appear to belong to the chemokine receptor family, but for which no endogenous ligand has yet been identified (purple); and (4) 'non-signaling' – receptors that bind endogenous chemokines but do not as yet have an associated signal transduction event (blue). Endogenous chemokine receptor ligands are shown in black. Some virally encoded chemokine receptor antagonists are shown in red; note the broad spectrum of receptors that are regulated by vMIP-II (vMIP-II is represented in a smaller font size to indicate those receptors at which it exhibits only partial antagonism). Virally encoded chemokines that are agonists at indicated receptors are shown in green. Abbreviations: BCA-1/CXCL13, B-cell-attracting chemokine 1; CTACK/CCL27, cutaneous T-cell attracting chemokine; DARC, Duffy antigen receptor for chemokines; ELC/CCL19, Epstein–Barr virus-induced receptor ligand chemokine; ENA78/CXCL5, epithelial cell-derived neutrohil-activating factor 78; GCP-2/CXCL6, granulocyte chemoattractant protein 2; HCC-1/CCL14, hemofiltrate CC chemokine 1; HCR, human chemokine receptor; IL-8/CXCL8, interleukin 8; IP-10/CXCL10, interferon-inducible protein 10; I-TAC/CXCL11, interferon-inducible T-cell α chemoattractant; LARC/CCL20, liver and activation-related chemokine; MCP-1/CCL2, monocyte chemoattractant protein 1; MDC/CCL22, macrophage-derived chemokine; MIG/CXCL9, monocyte-induced by γ-interferon; MIPF-1/CCL23, myeloid progenitor inhibitory factor 1; NAP-2/CXCL7, neutrophil-activating peptide 2; RANTES/CCL5, regulation on activation of normal T cells expressed and secreted; SDF-1/CXCL12, stromal cell-derived factor 1; SLC/CCL21, second lymphoid tissue chemokine; TARC/CCL17, T cell and activation-related chemokine; TECK/CCL25, thymus expressed chemokine; vMIP-II, virally encoded macrophage inflammatory protein II.

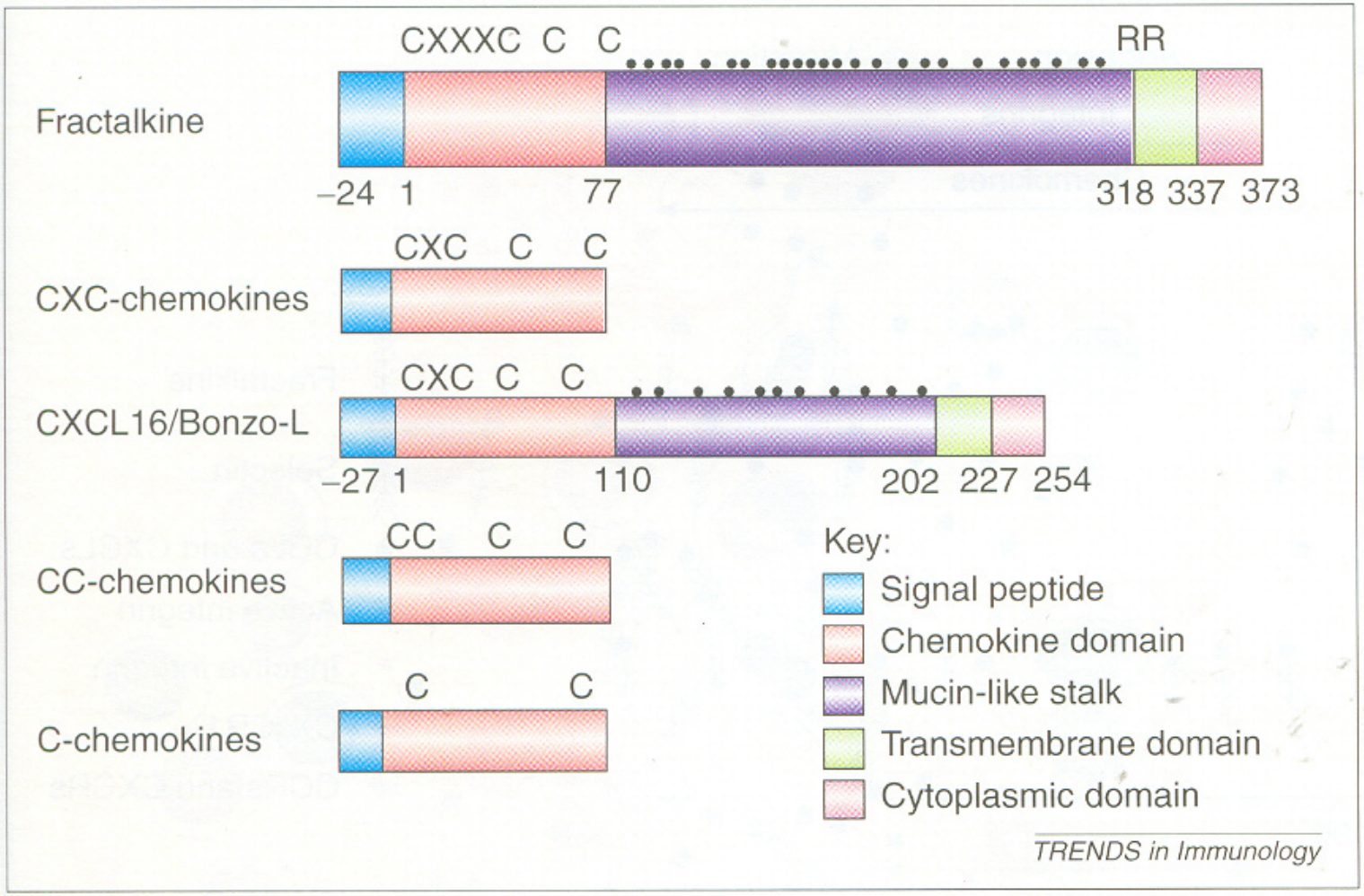


Fig. 1. Schematic structure of fractalkine. Fractalkine is a large protein of 373 amino acids containing multiple domains and is structurally distinct from the CXC-, CC- and C-chemokines. Beginning with the predicted signal peptide, fractalkine comprises an N-terminal chemokine domain (residues 1–76) with a unique three-residue insertion (CX_3C), a mucin-like stalk (residues 77–317) with predicted *O*-glycosylated serine and threonine residues (●), a transmembrane domain (residues 318–336) and an intracellular domain (residues 337–373). RR is a membrane-proximal dibasic motif similar to a dibasic cleavage site in syndecans. The recently reported CXCL16 chemokine has several features in common with fractalkine and is predicted to be membrane bound.

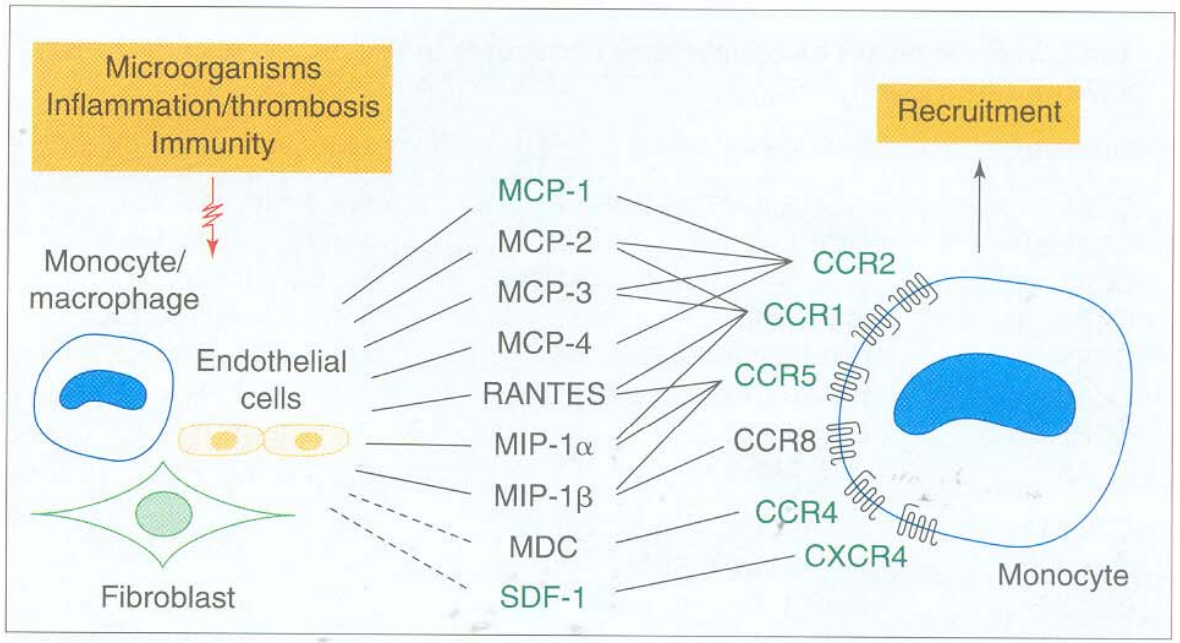


Fig. 2. *Monocyte recruitment as a robust output of the chemokine system. Resting or stimulated mononuclear phagocytes and stromal cells (endothelial cells, fibroblasts) concomitantly produce many cytokines (polyspeirism) whose spectrum of action includes monocytes. Production is constitutive (dashed line) or inducible (unbroken line). Monocytes express several chemokine receptors that are recognized in a promiscuous way. Green labels indicate that knockout mice or deficient humans (Δ32 CCR5) have been studied. The system is built so that inactivation of any single component (agonist or receptor) allows a minimal level of phagocyte trafficking sufficient for fundamental functions, such as tissue remodeling, clearance of debris and innate resistance. Abbreviations: MCP-1 (CCL2), monocyte chemotactic protein 1; MDC (CCL22), macrophage-derived chemokine; MIP-1α (CCL3), macrophage inflammatory protein 1α; SDF-1 (CXCL12), stromal cell-derived factor 1.*

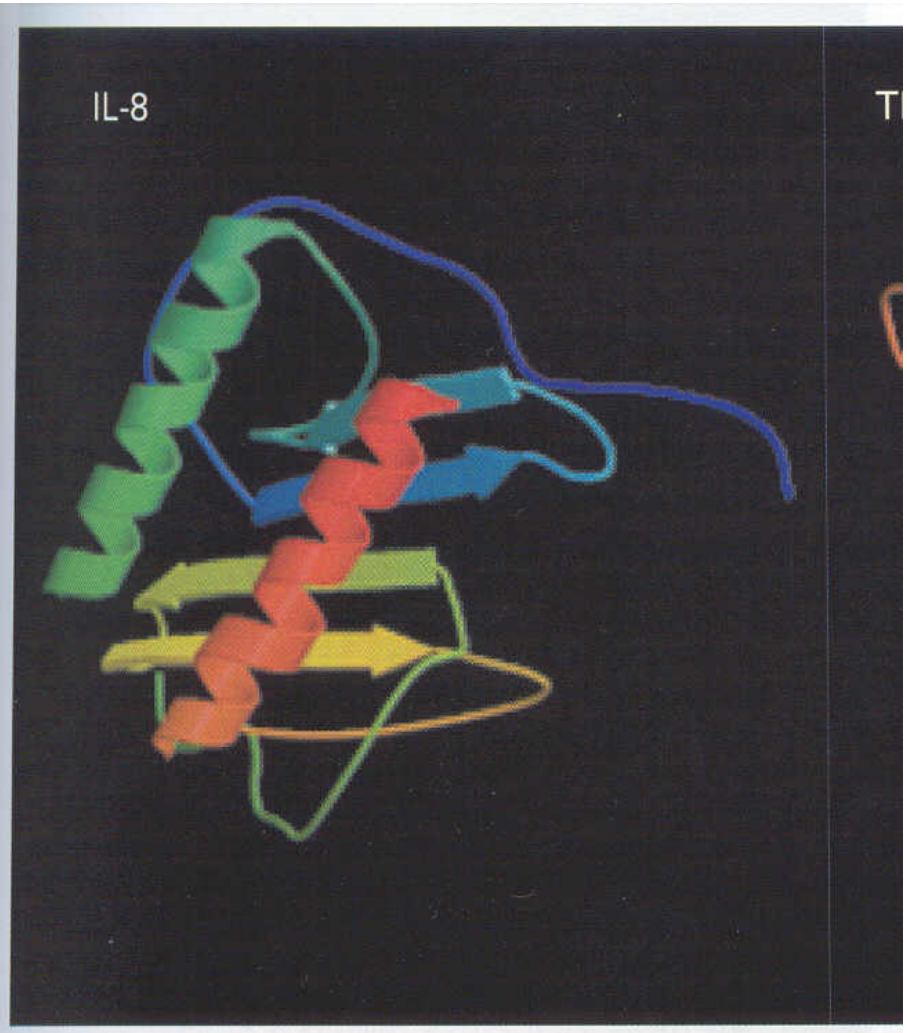


Fig. 7.4 IL-8 has a common structure, shared with many chemokines. The cytokine is shown in its normal dimeric form with two sections of α-helix lying above a region of β-pleated sheet. This bears a remarkable resemblance to the binding groove of the MHC molecules. Many chemokines attach to extracellular matrix via sites in the α-helix and to their specific receptors via sites in the β-sheet. TNFα is shown in its normal trimeric form. Note that many cytokines have their effects by polymerizing their receptors at the cell surface, thus TNF and related molecules trimerize their receptors.

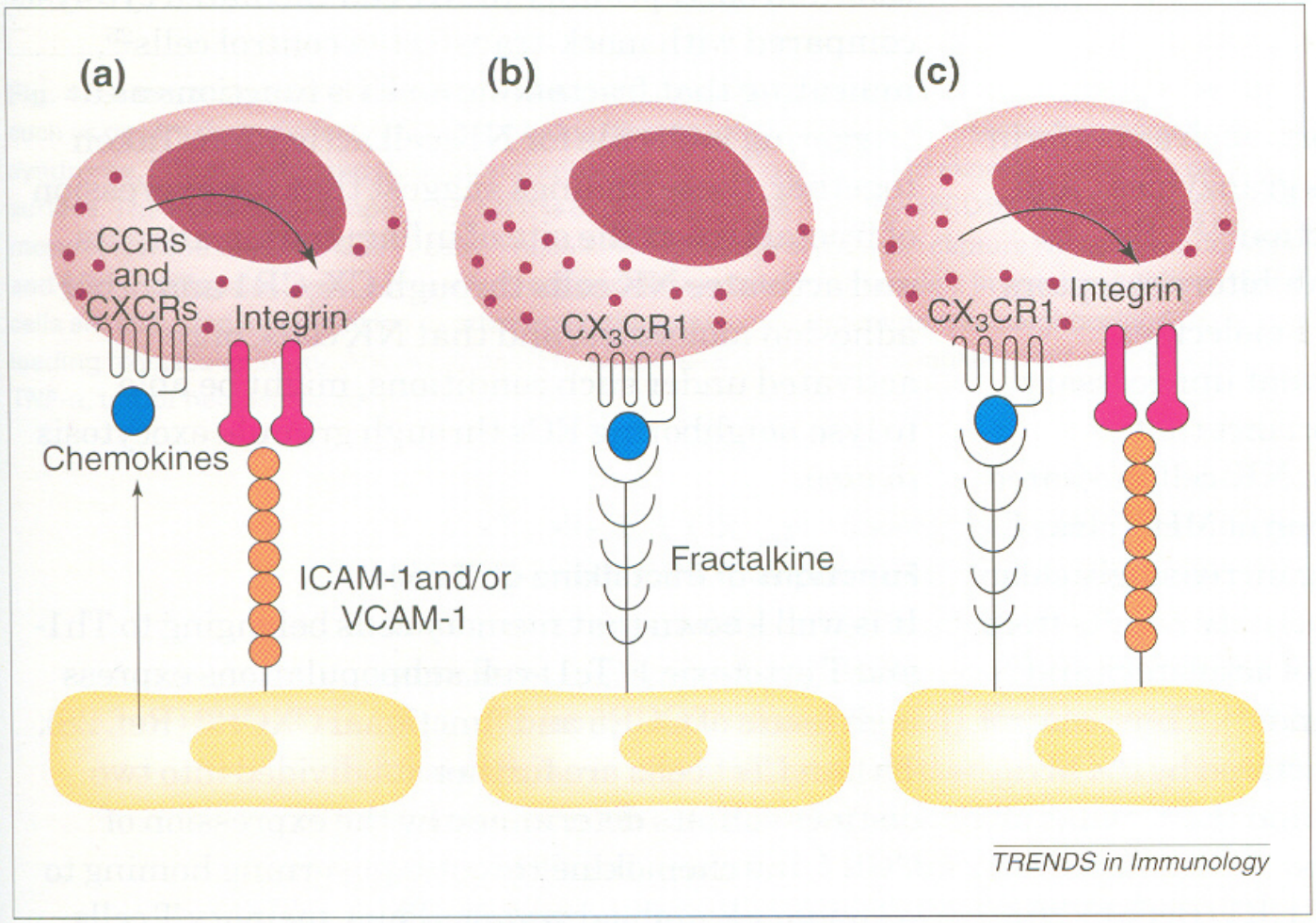


Fig. 2. Dual function of fractalkine as an adhesion molecule and chemokine. (a) Soluble chemokines bind to specific CC- or CXC-chemokine receptors (CCRs or CXCRs) and trigger integrin activation. Integrins bind with high avidity to their ligands (ICAM-1 or VCAM-1) and support cell adhesion. (b) Fractalkine, consisting of a chemokine domain and mucin-like stalk, is expressed as a membrane-bound form on activated endothelial cells. Interaction between fractalkine and its receptor, CX_3CR1, can support cell adhesion without the involvement of integrins. (c) In addition to the intrinsic adhesive function of fractalkine, CX_3CR1 can also transduce signals for integrin activation. Therefore, fractalkine and integrins mediate cell adhesion cooperatively. Abbreviations: ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1.

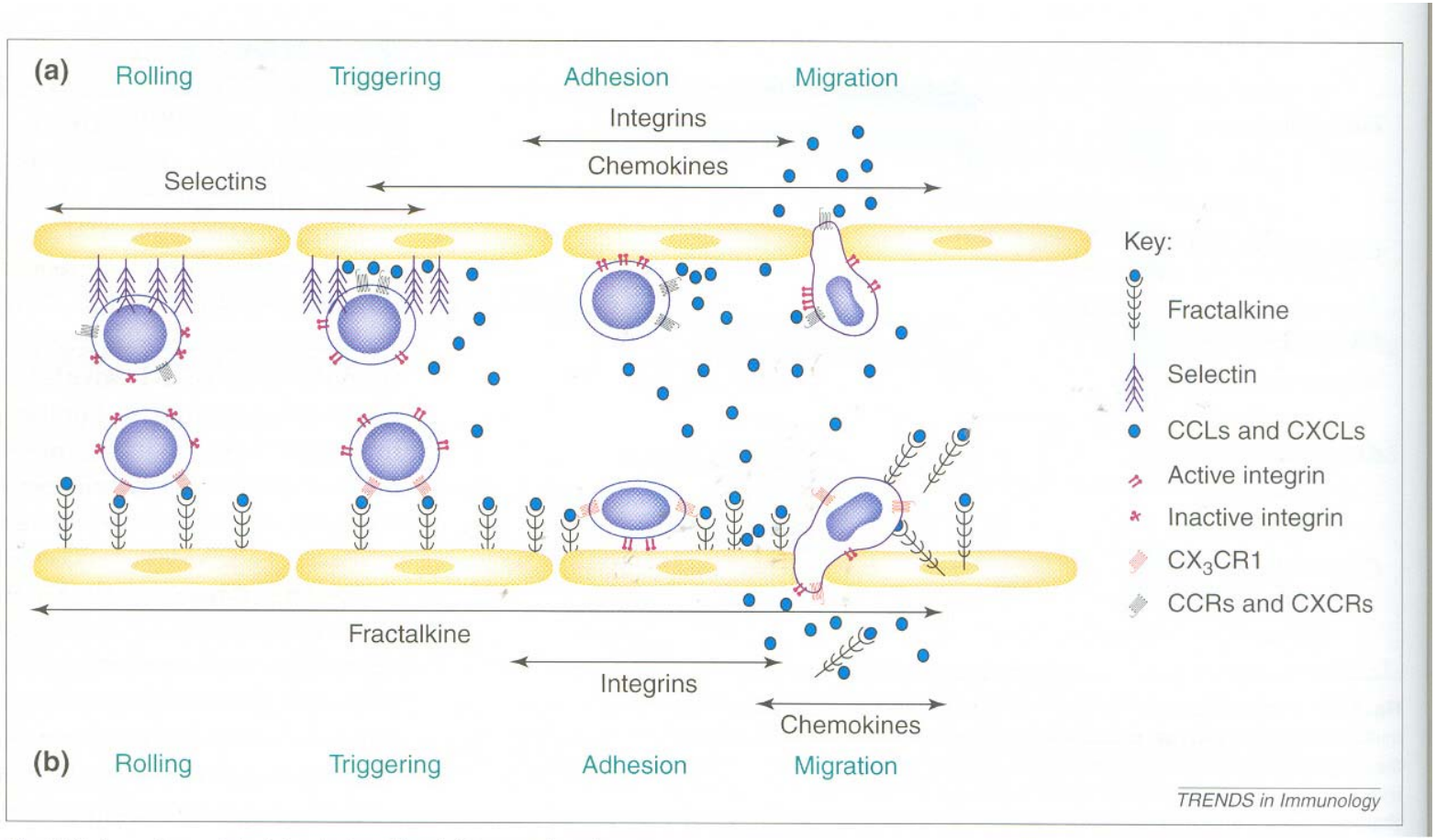


Fig. 3. Schematic model of classical and fractalkine-mediated pathways in the adhesion cascade. Leukocyte migration from the circulation into the peripheral tissue is a stepwise process. (a) The classical pathway. The first step involves transient, weak, selectin-mediated binding (rolling). Next, integrins on leukocytes are activated by chemokines that have been presented on glycosaminoglycans (triggering), resulting in firm adhesion between leukocytes and endothelial cells (adhesion). Finally, leukocytes migrate through the endothelial layer in response to a chemokine gradient (migration). (b) The fractalkine-mediated pathway. Fractalkine is expressed on endothelial cells as the membrane-bound form and captures leukocytes in a selectin- and integrin-independent manner. Interaction between fractalkine and its receptor, CX_3CR1, can increase integrin avidity also, resulting in firm adhesion. Leukocytes then extravasate through the vascular wall and into the tissue in response to a chemokine gradient.

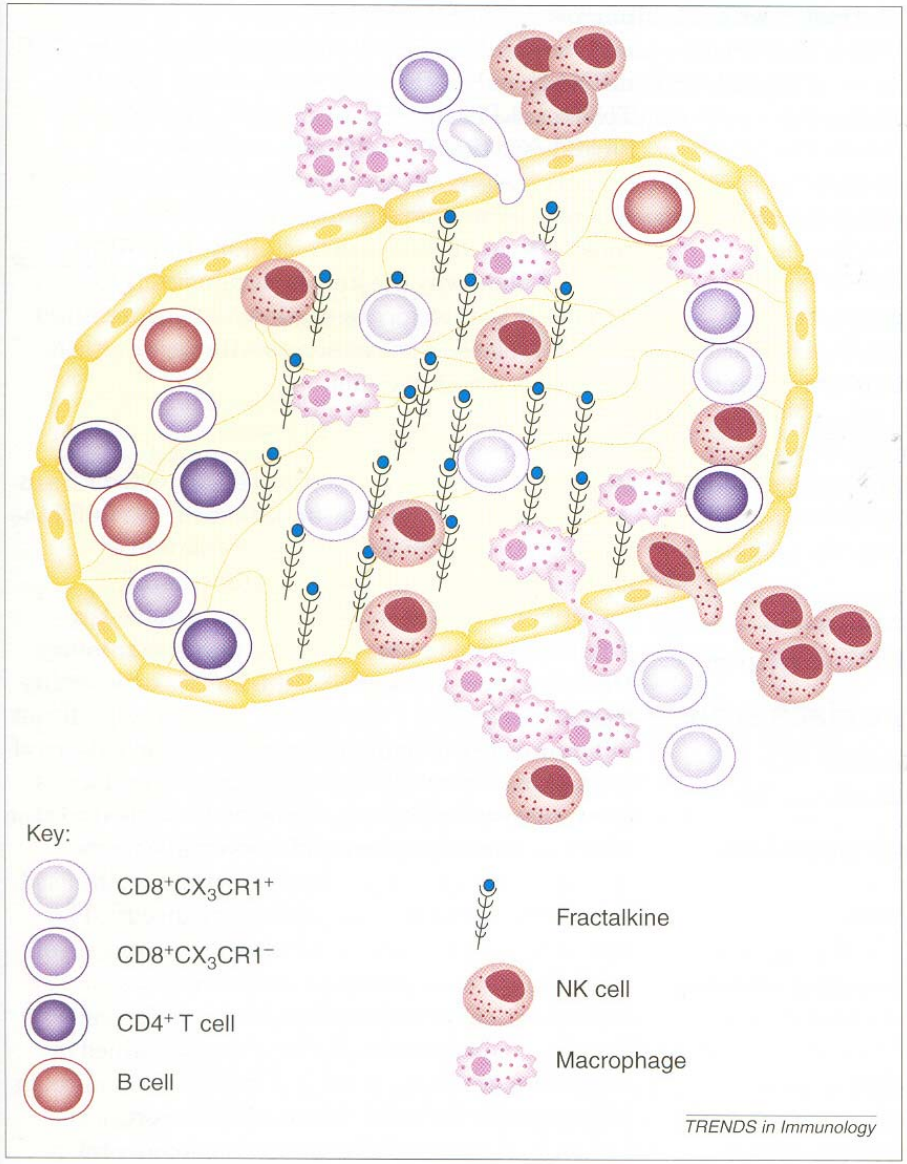


Fig. 4. Schematic model of fractalkine-mediated vascular injury. Following an inflammatory insult, such as occurs during infections, autoimmune disease, graft-versus-host disease and vascular leak syndrome, ECs are activated through stimulation with TNF-α or IL-1, and express fractalkine on their surface. The fractalkine receptor, CX_3CR1, is expressed on the majority of $CD16^+$ NK cells and $CD14^+$ monocytes, and on some $CD8^+$ T cells. Fractalkine expressed on ECs can capture NK cells, monocytes and $CD8^+$ T cells selectively, especially those possessing cytolytic granules. In some conditions, these cells are activated by fractalkine or other activating molecules and might lyse neighboring ECs, leading to vascular injury. Abbreviations: EC, endothelial cell; IL-1, interleukin-1; NK, natural killer; TNF-α, tumor necrosis factor α.

CÉLULAS DENDRÍTICAS

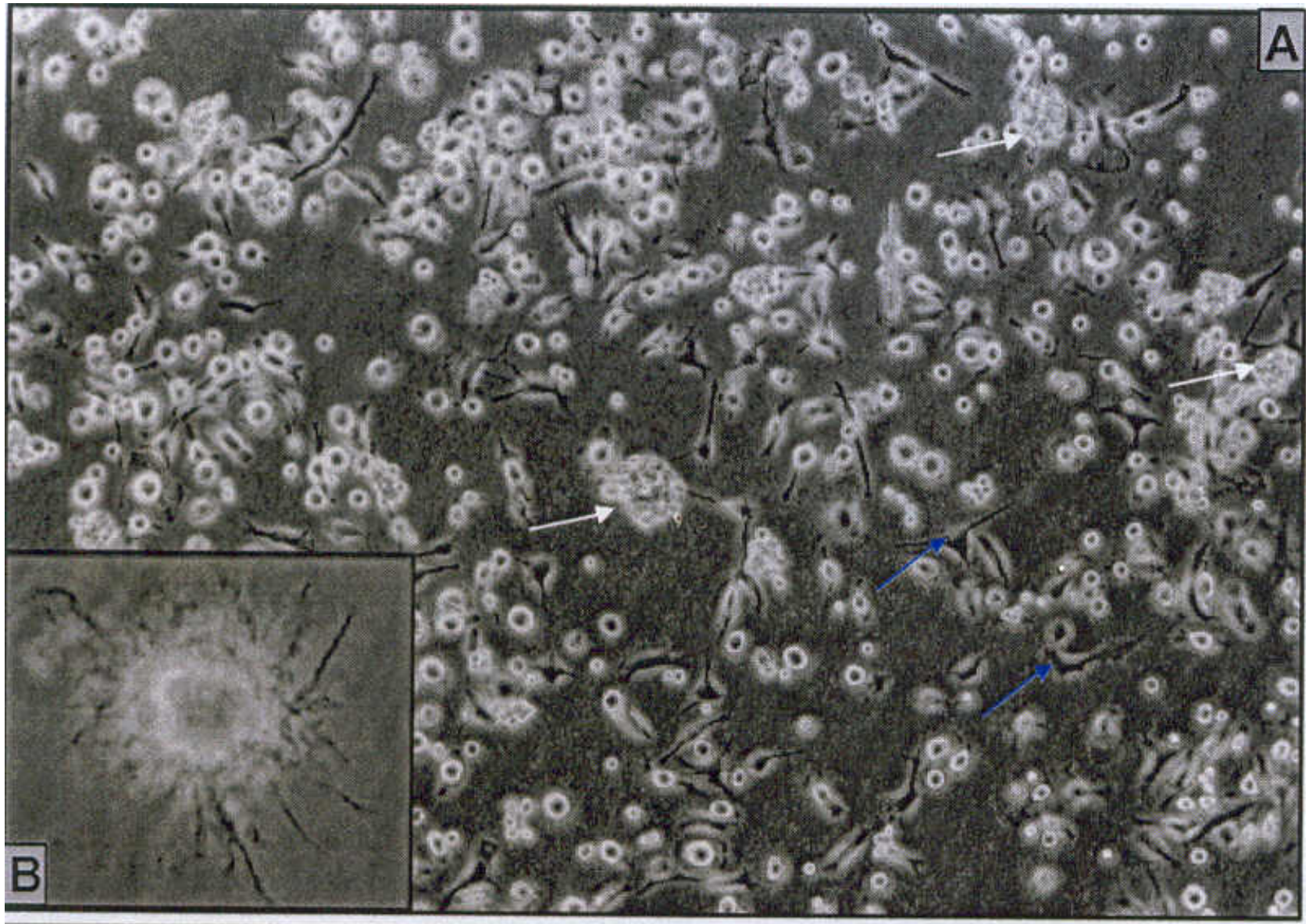
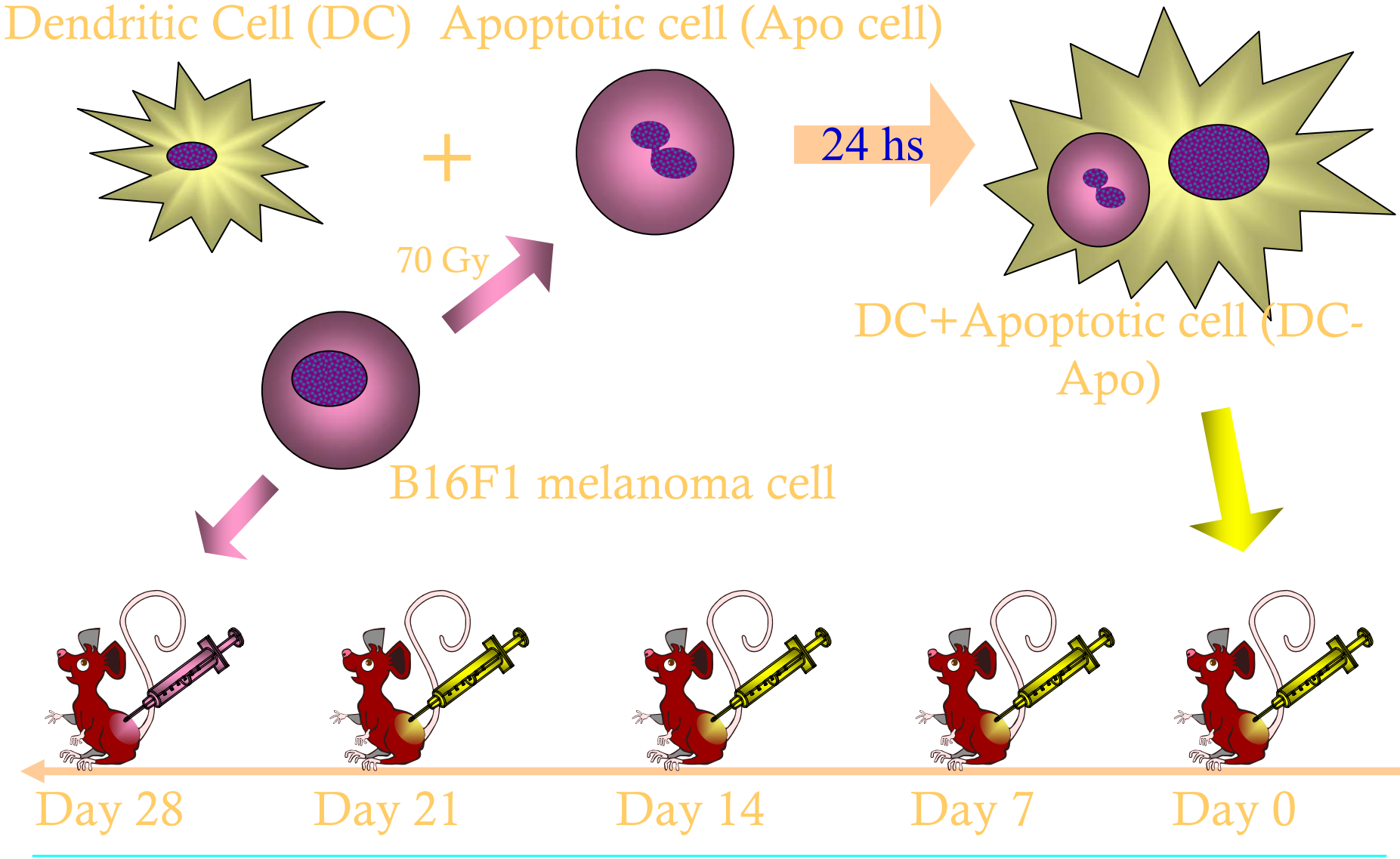
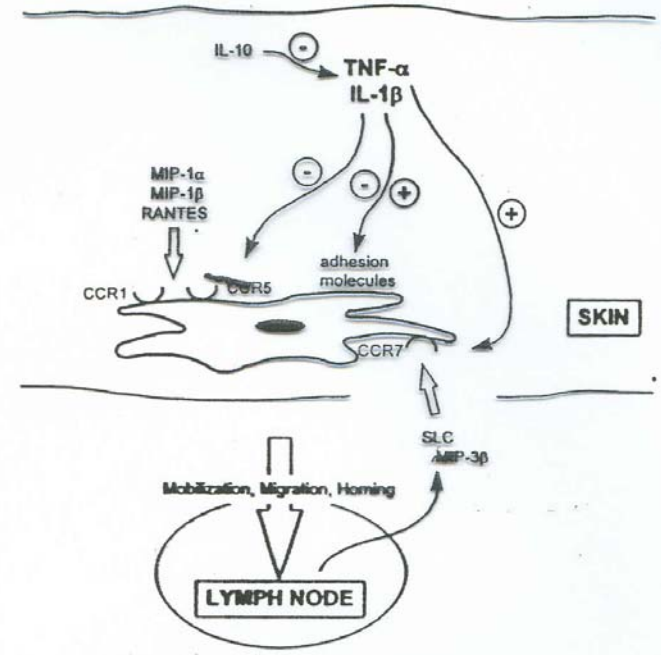


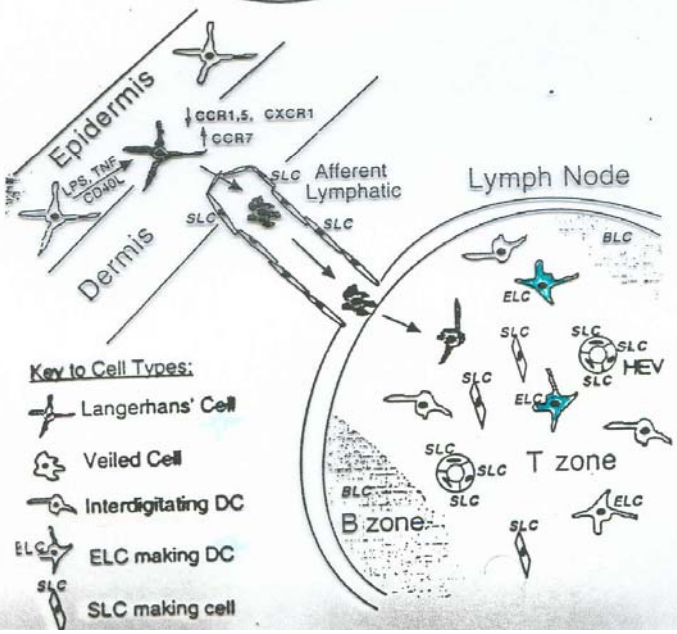
Figura 2: CD obtenidas a partir de precursores de médula ósea luego de 7 días de cultivo. *(A)* La flecha blanca indica los *clusters* de CD, la azul señala los macrófagos adheridos a la placa. Aumento original 200x. *(B)* CD. Aumento original 1000x.

Experimental design



HOMING DE CELULAS DE LANGERHANS





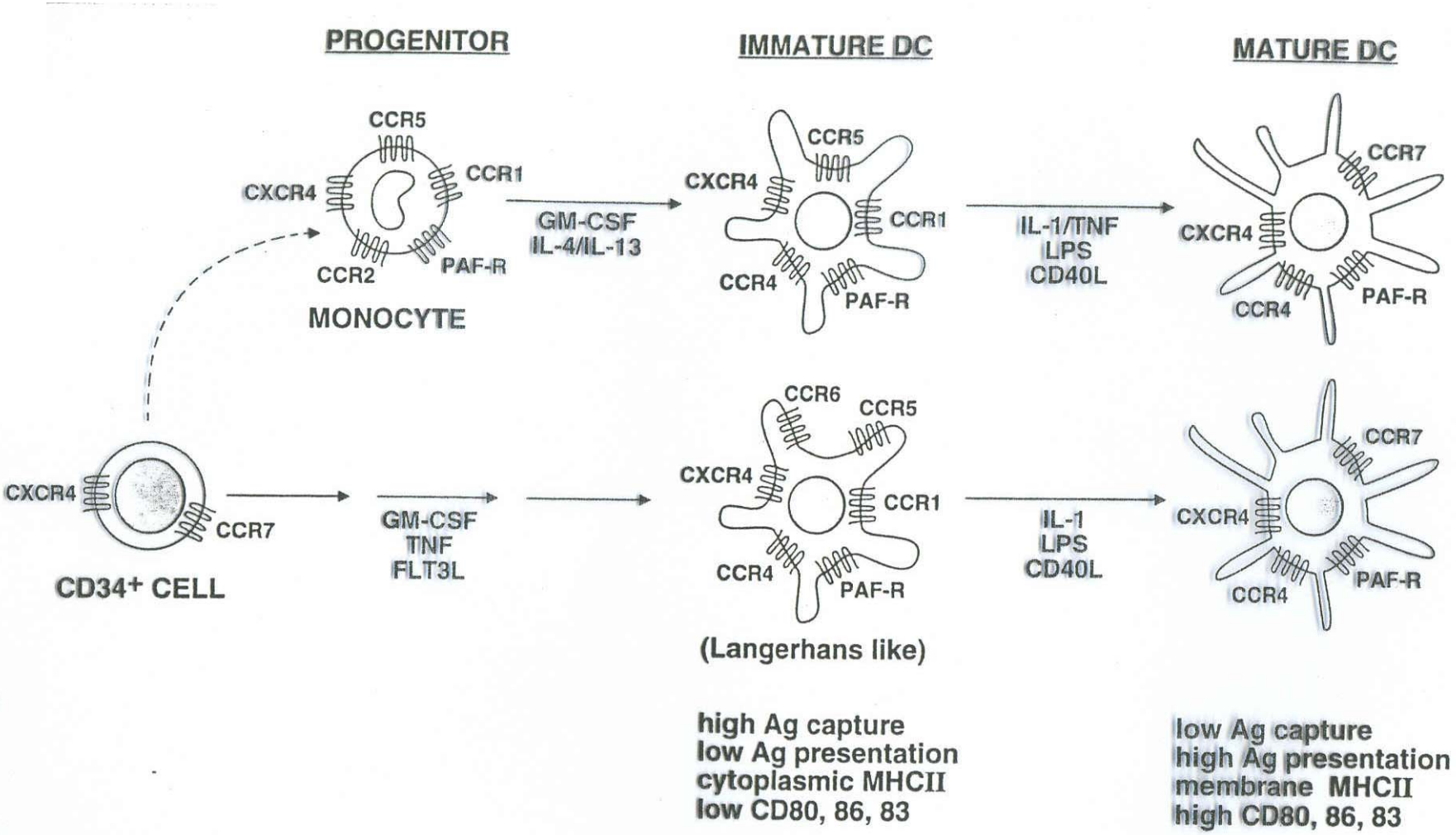


Fig. 1. Functional chemokine receptor expression in DC subsets and at different stages of maturation. Mono-DC and CD34-DC share the same repertoire with the exception of CCR6, which is selectively expressed in CD34-DC. Maturation of DC with inflammatory and immune stimuli induce expression of CCR7 and of increased levels of PAF receptor (PAF-R). Mature DC express also CXCR4 and low levels of CCR4. Low CCR4 expression appears to be functionally relevant, as demonstrated by the chemotactic effect of MDC. Mature DC have down-modulated CCR1, CCR5, and CCR6 and fail to migrate to their agonists.

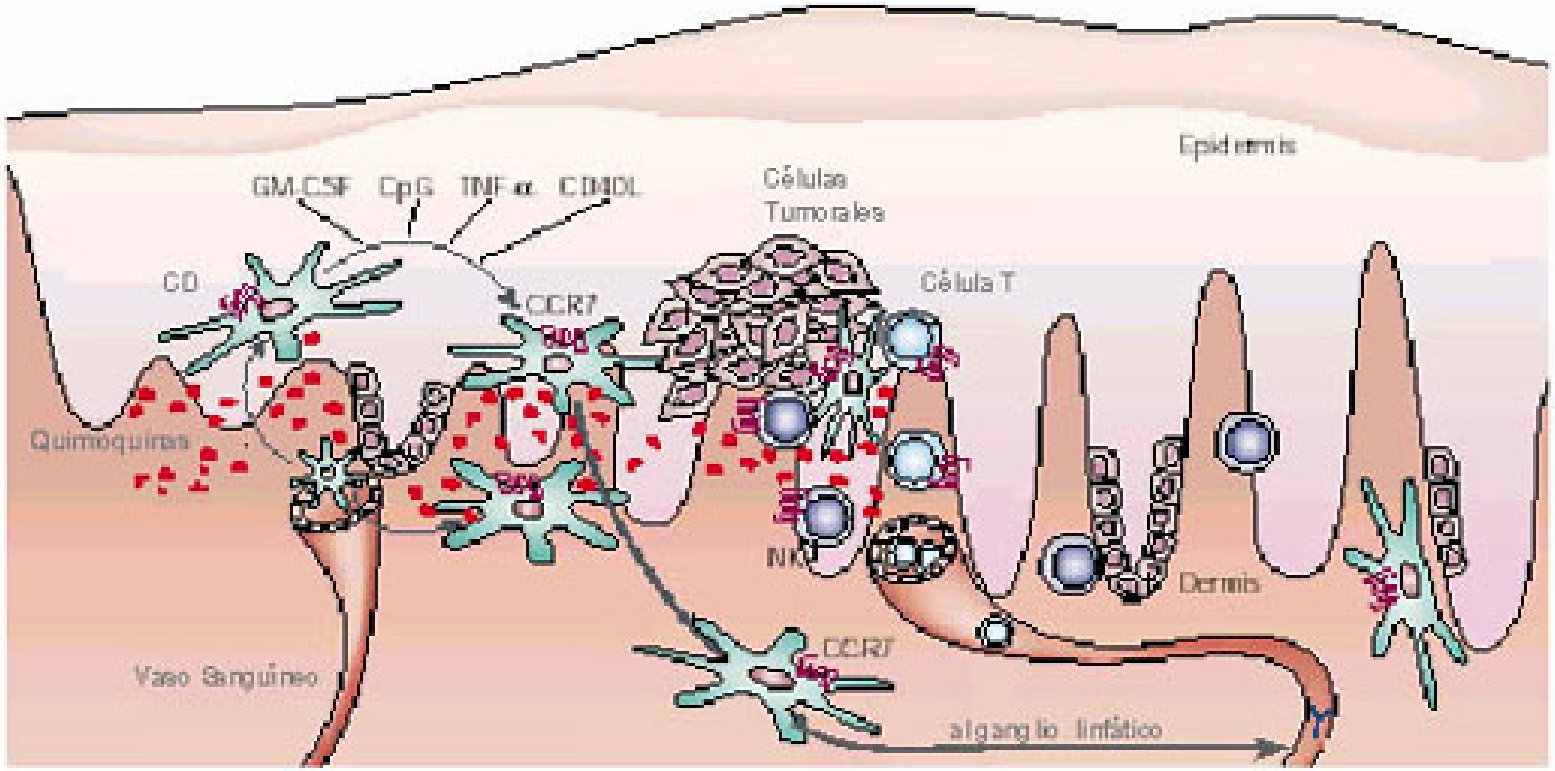


FIGURA 3: Las células dendríticas, después de captar el antígeno y madurar con GM-CSF, CpG, TNFα, CD40L, expresan el receptor CCR7 y migran hacia los ganglios linfáticos donde presentan el antígeno a las c{elulas T . Las células T activadas específicamente por el antígeno, producen la citoquina IL-2, que induce la proliferación de las células T en células memoria / efectoras. Las células T memoria específicas recirculan y utilizan mecanismos mediados por quimioquinas para extravasarse a los sitios de injuria, infección o crecimiento tumoral.
CD40L: ligando de CD40; CpG: secuencia inmunoestimulatoria de DNA; ; CD: célula dendrítica; GM-CSF: factor estimulador de colonias de granulocitos y macrófagos; TNF: factor de necrosis tumoral

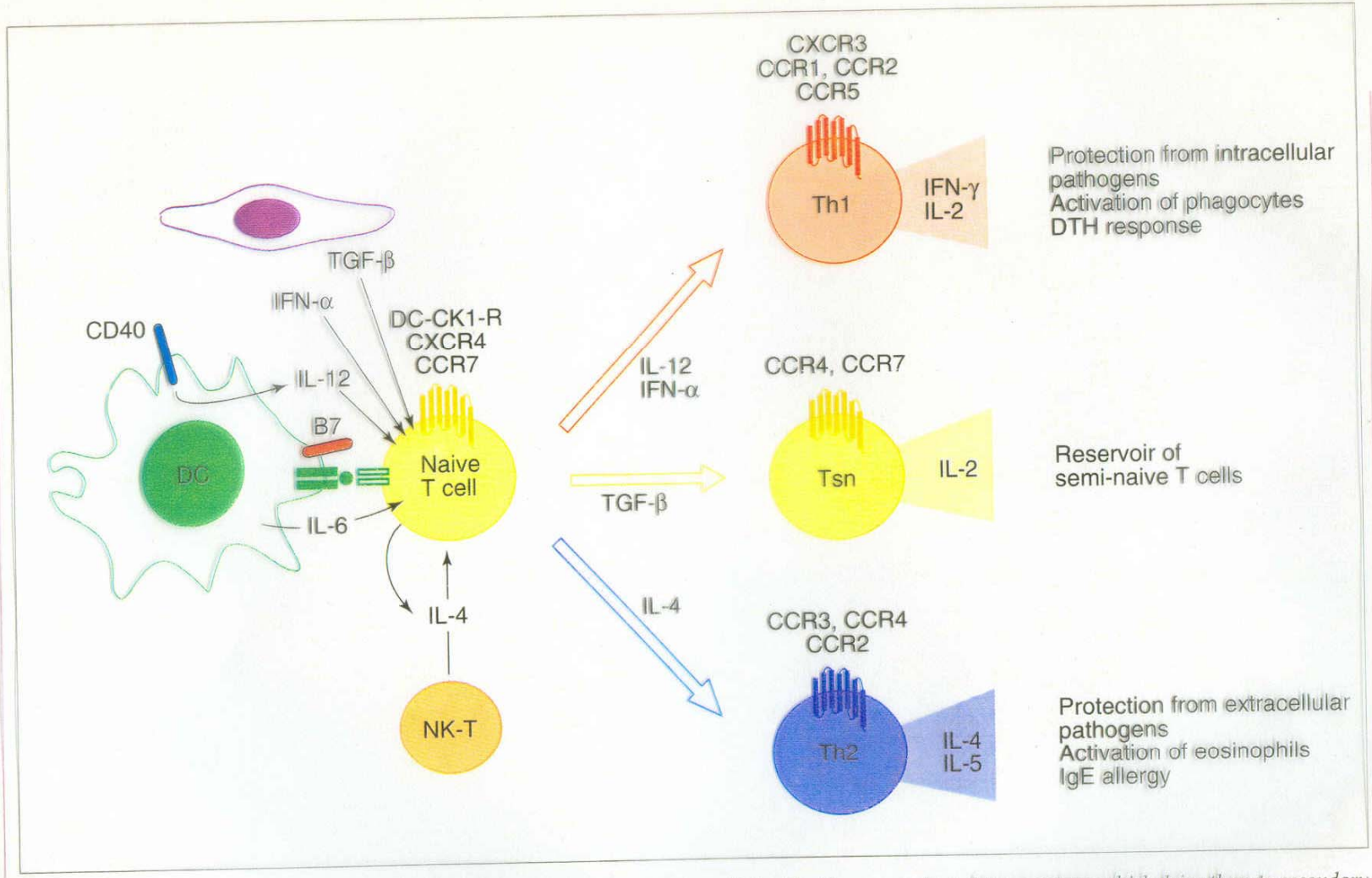


Fig. 2. *T-cell polarization results in selective expression of chemokine receptors. Naive T cells express chemokine receptors which drive them to secondary lymphoid organs and promote their interaction with dendritic cells (DCs). Cytokines present at the site of priming determine polarization of activated T cells. IL-12, produced by DCs stimulated via CD40, as well as interferon α (IFN-α), drive T helper 1 (Th1)-cell polarization. Interleukin 4 (IL-4) produced by naive T cells under the influence of DC-derived IL-6 or by bystander cells (NK1.1 T cells or mast cells) drives Th2-cell polarization. Transforming growth factor β (TGF-β) produced at high levels in some tissues, prevents Th2 polarization and maintains the activated T cells in a semi-naive state (Tsn). Polarized T cells produce different sets of cytokines following antigenic stimulation and express different sets of chemokine receptors. Abbreviations: DC-CK1-R, dendritic cell chemokine 1 receptor; DTH, delayed-type hypersensitivity; NK-T, natural killer T cell.*

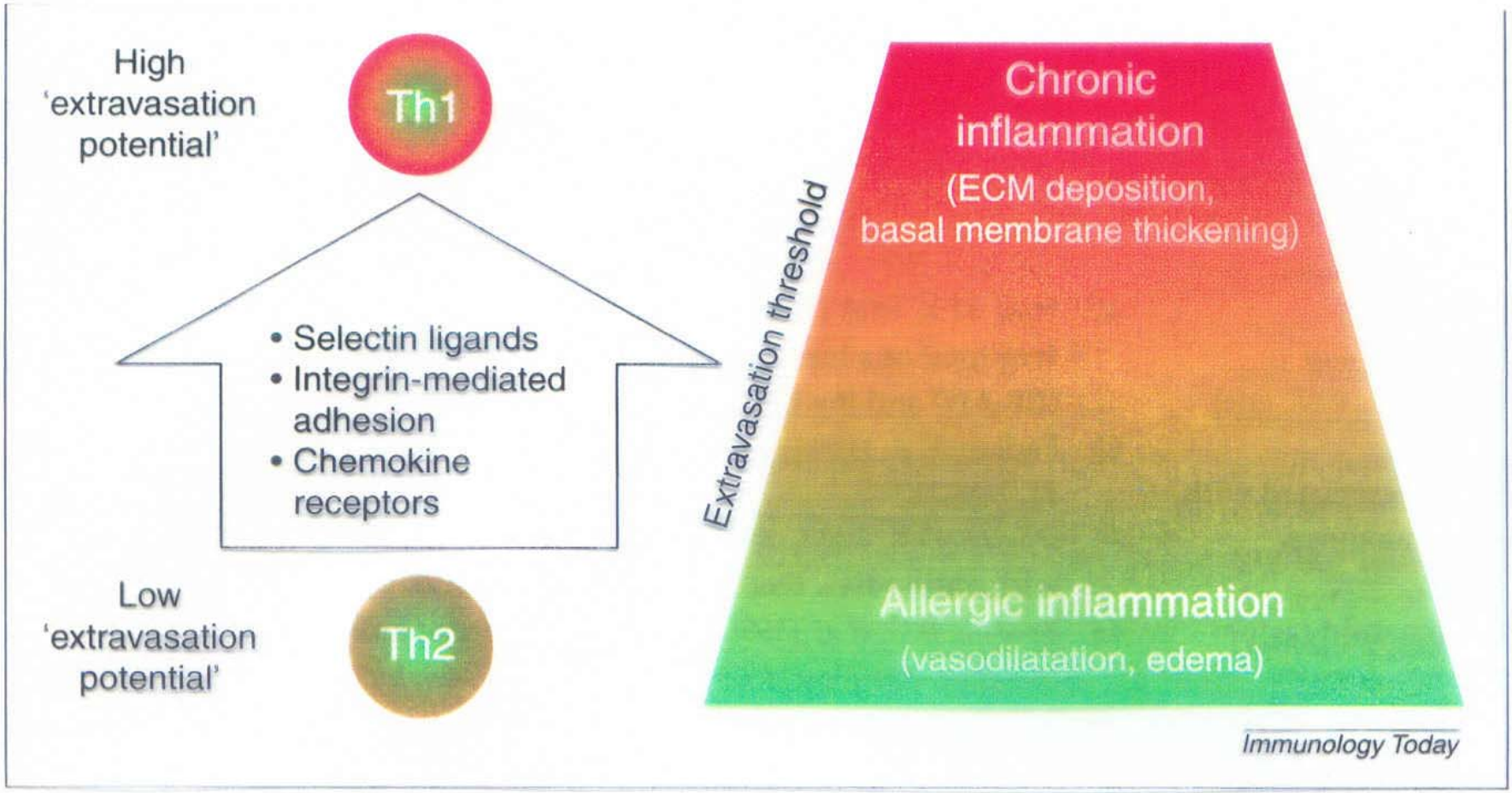


Fig. 1. *Selective thresholds for T helper (Th)-cell extravasation. A model to integrate the molecular mechanisms involved in differential recruitment of Th cell subsets with the putative inflammation-regulated threshold for leukocyte extravasation. Abbreviations: ECM, extracellular matrix; Th1, T helper 1 cell.*

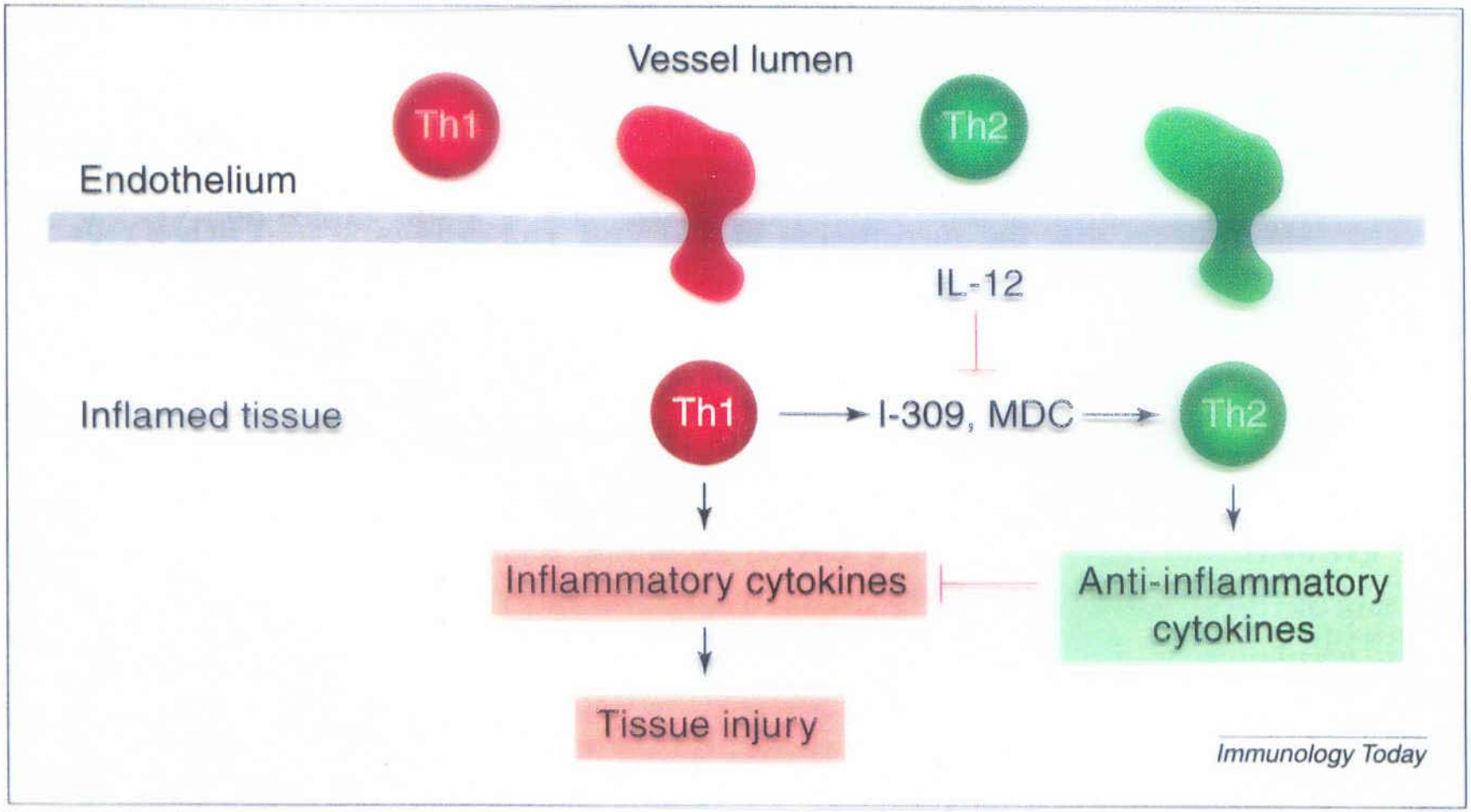


Fig. 2. *T helper (Th) cells, chemokines and homeostasis. A schematic view of the potential homeostatic role that chemokines, such as macrophage-derived chemokine (MDC) and I-309 produced by activated Th1 cells, may play by recruiting anti-inflammatory Th2 cells. The red bar indicates the inhibitory effect of interleukin 12 (IL-12) on I-309 and MDC produced by activated Th1 cells.*

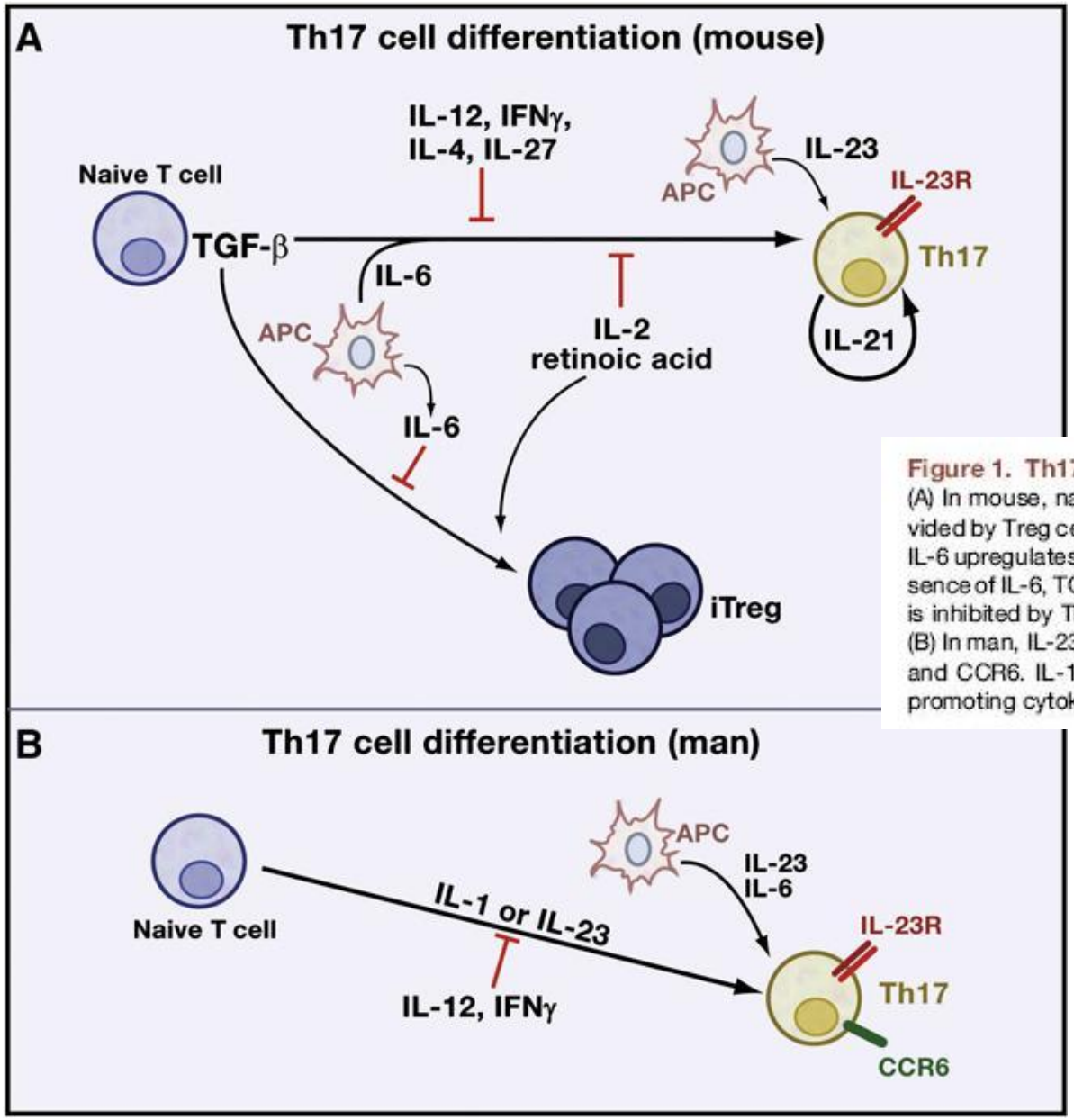


Figure 1. Th17 Cell Differentiation in Mouse and Man

(A) In mouse, naive T cells activated in the presence of TGF-β (possibly provided by Treg cells) and IL-6 begin differentiation toward the Th17 cell subset; IL-6 upregulates IL-21 and IL-23R to further their Th17 development. In the absence of IL-6, TGF-β instead induces regulatory T cells. Th17 cell development is inhibited by Th1 and Th2 cytokines, as well as IL-2 and retinoic acid.

(B) In man, IL-23 or IL-1 drives differentiation of Th17 cells that express IL23R and CCR6. IL-1's effects may be enhanced by IL-23 and/or IL-6. Th1-cell-promoting cytokines inhibit Th17 cell development.

QUIMIOQUINAS MACROFAGOS Y TUMORES

MCP-1 y TUMORES

Targeting Tumor-Associated Macrophages and Inhibition of MCP-1 Reduce Angiogenesis and Tumor Growth in a Human Melanoma Xenograft

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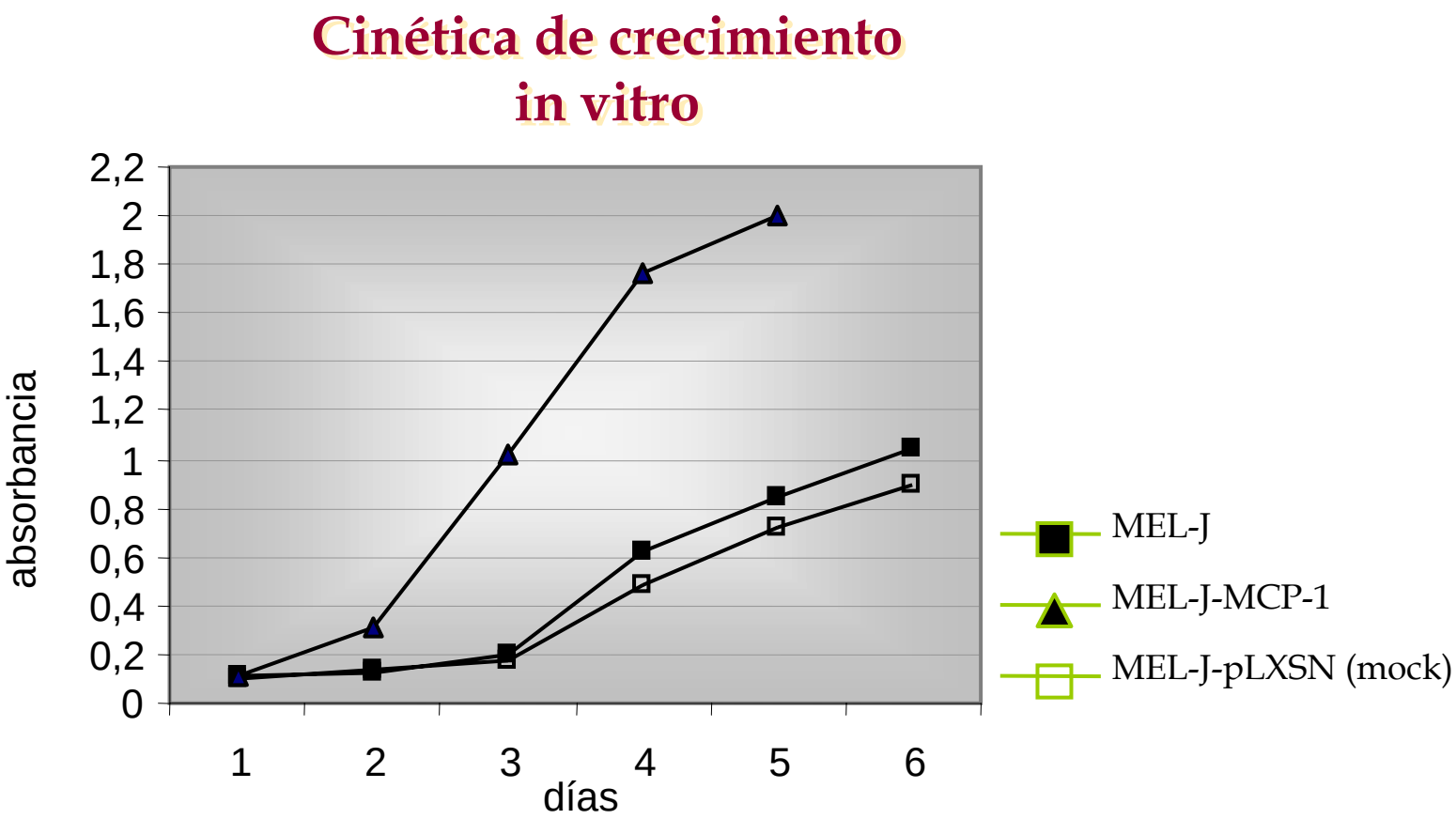
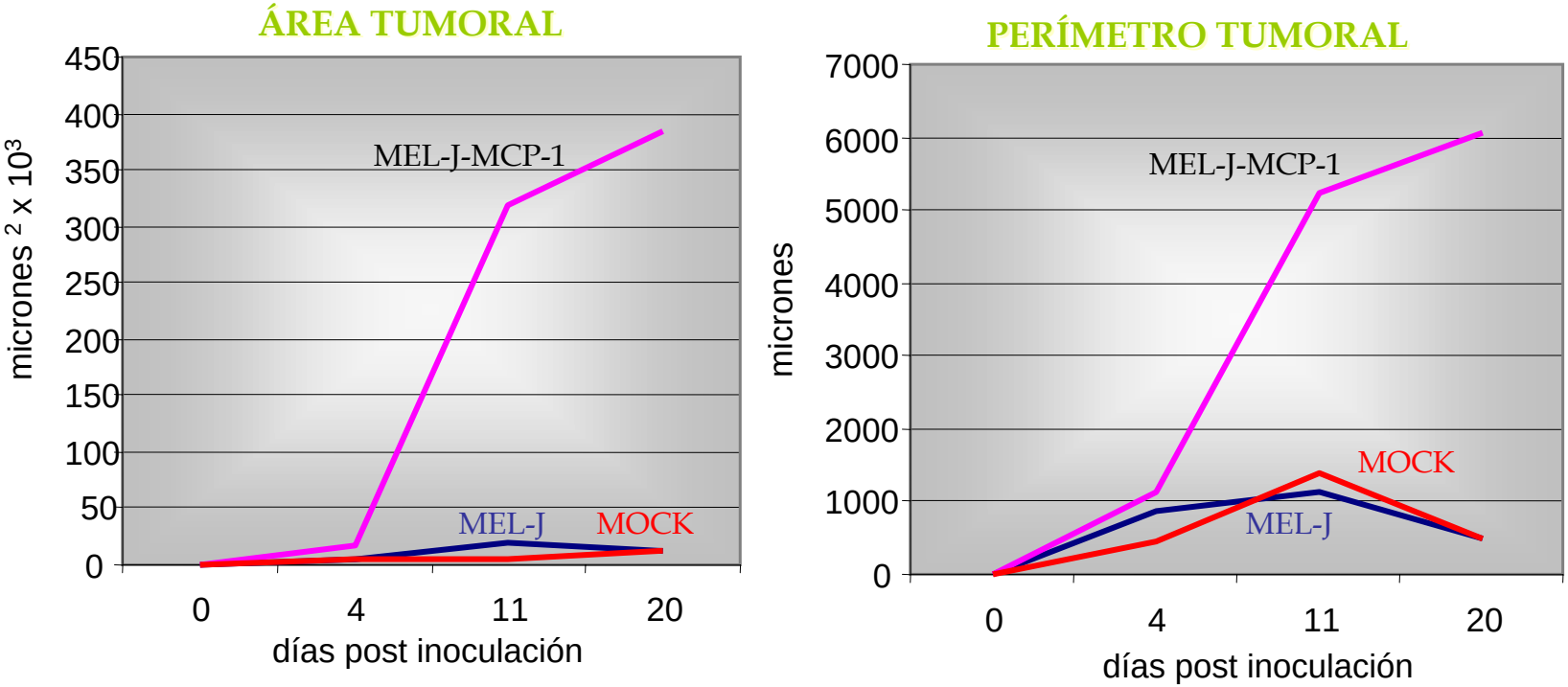


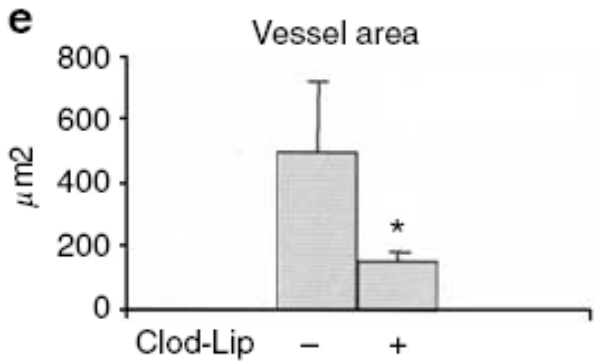
Curva de crecimiento de las distintas sublíneas de melanoma.
Las células fueron desprendidas de las placas de cultivo con EDTA 1X, lavadas y 5000 células se plaquearon por cuadruplicado en placas de 96 pocillos. A los tiempos indicados, la cantidad de células vivas se cuantificó por tinción con MTT y lectura a DO 595 nm.

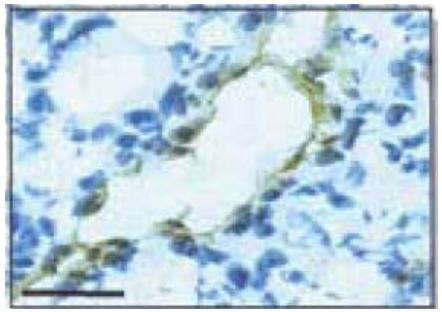
Comportamiento de los tumores in vivo

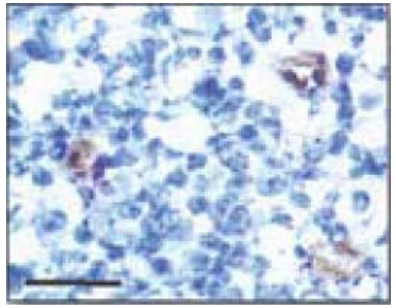


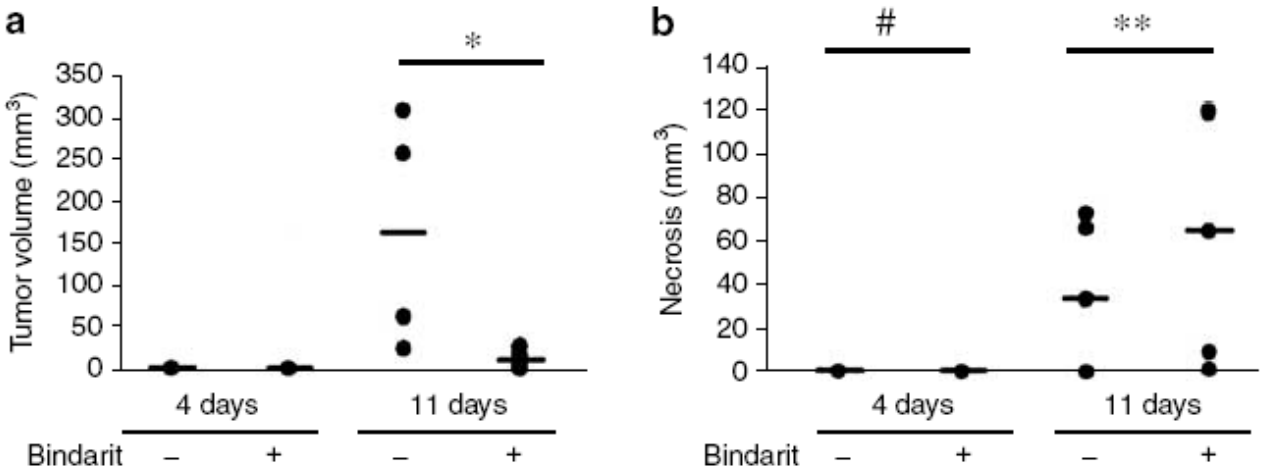
Curva de crecimiento in vivo.

1 x10^6 células de las las distintas sublíneas fueron inyectadas subcutáneamente en ratones nude. A distintos tiempos post inoculación, se extirparon los sitios de inyección y los tejidos se procesaron para el análisis histológico Las determinaciones se realizaron sobre secciones de tejido con un software para análisis de imágenes (Kontron Electronics)


e
Vessel area
800
600
400
200
0
μm2
*
Clod-Lip
–
+

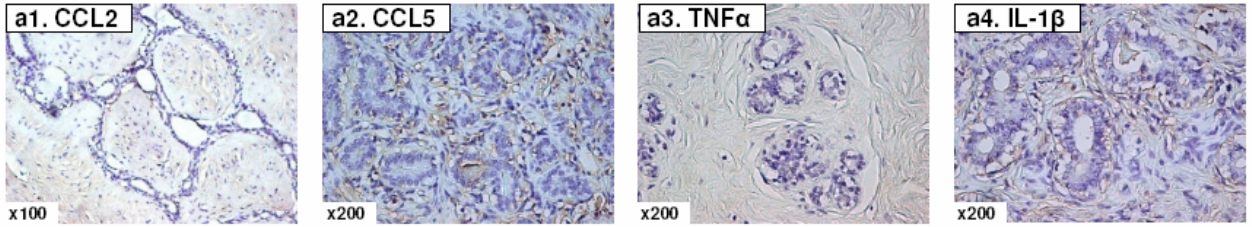




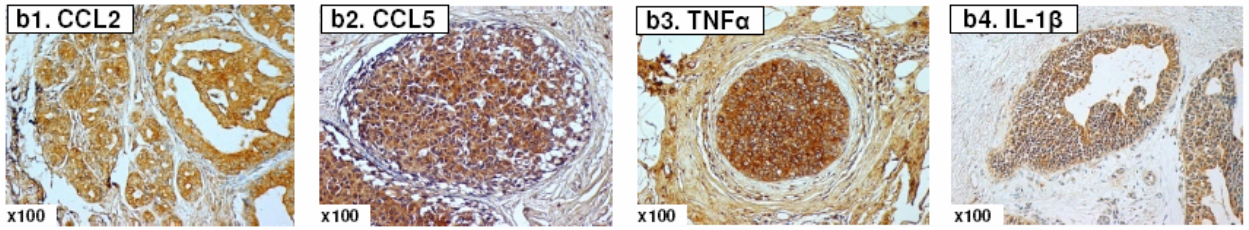

a
*
Tumor volume (mm3)
350
300
250
200
150
100
50
0
4 days
11 days
Bindarit – + – +
b
#
**
Necrosis (mm3)
140
120
100
80
60
40
20
0
4 days
11 days
Bindarit – + – +

- **Inflammatory mediators in breast cancer: Coordinated expression of TNFalpha &**
- **IL-1beta with CCL2 & CCL5 and effects on epithelial-to-mesenchymal transition**
- *BMC Cancer* 2011, **11**:130 doi:10.1186/1471-2407-11-130

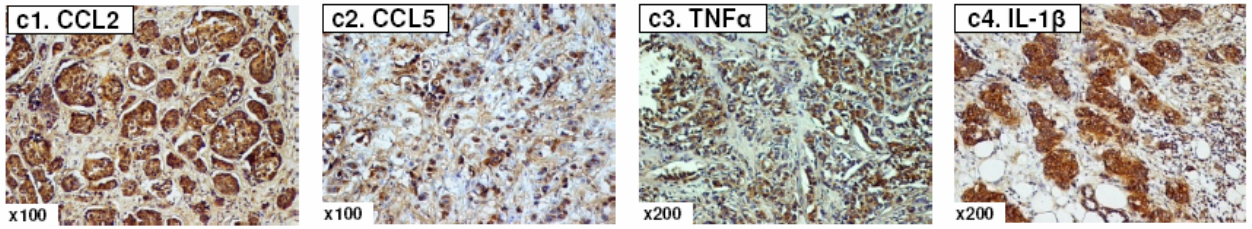
a. Benign Breast Diseases



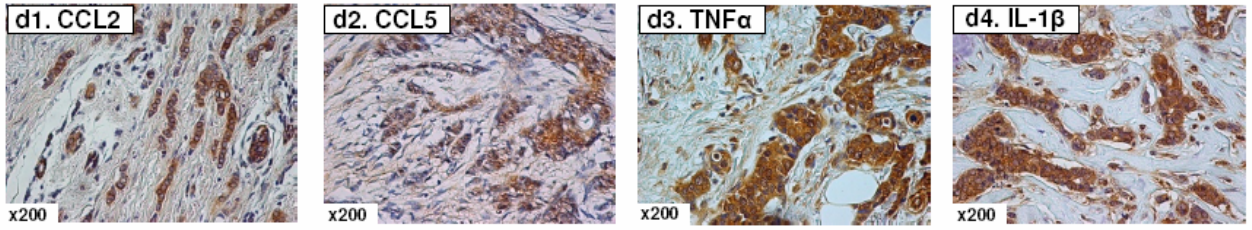
b. Ductal Carcinoma *In Situ*

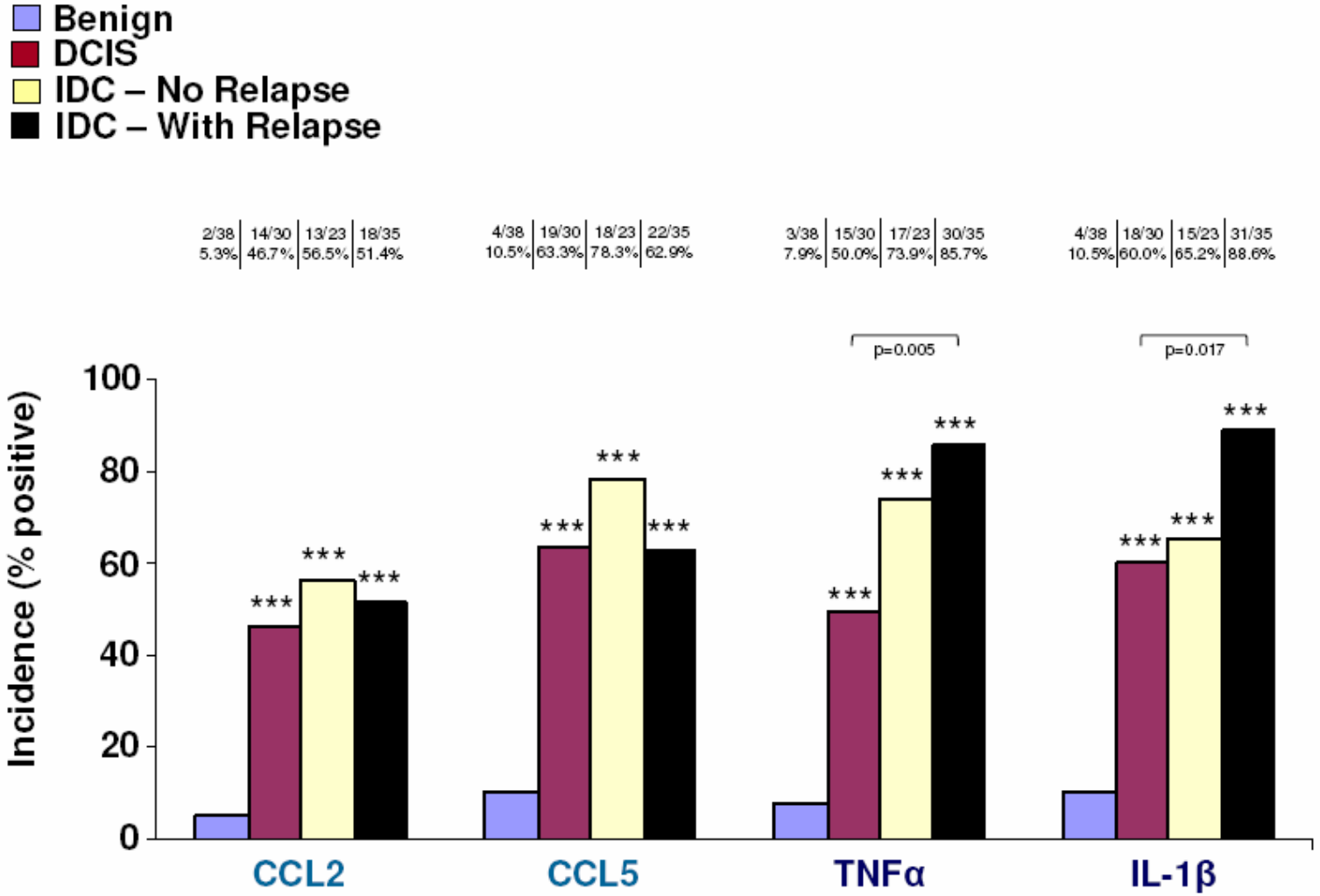


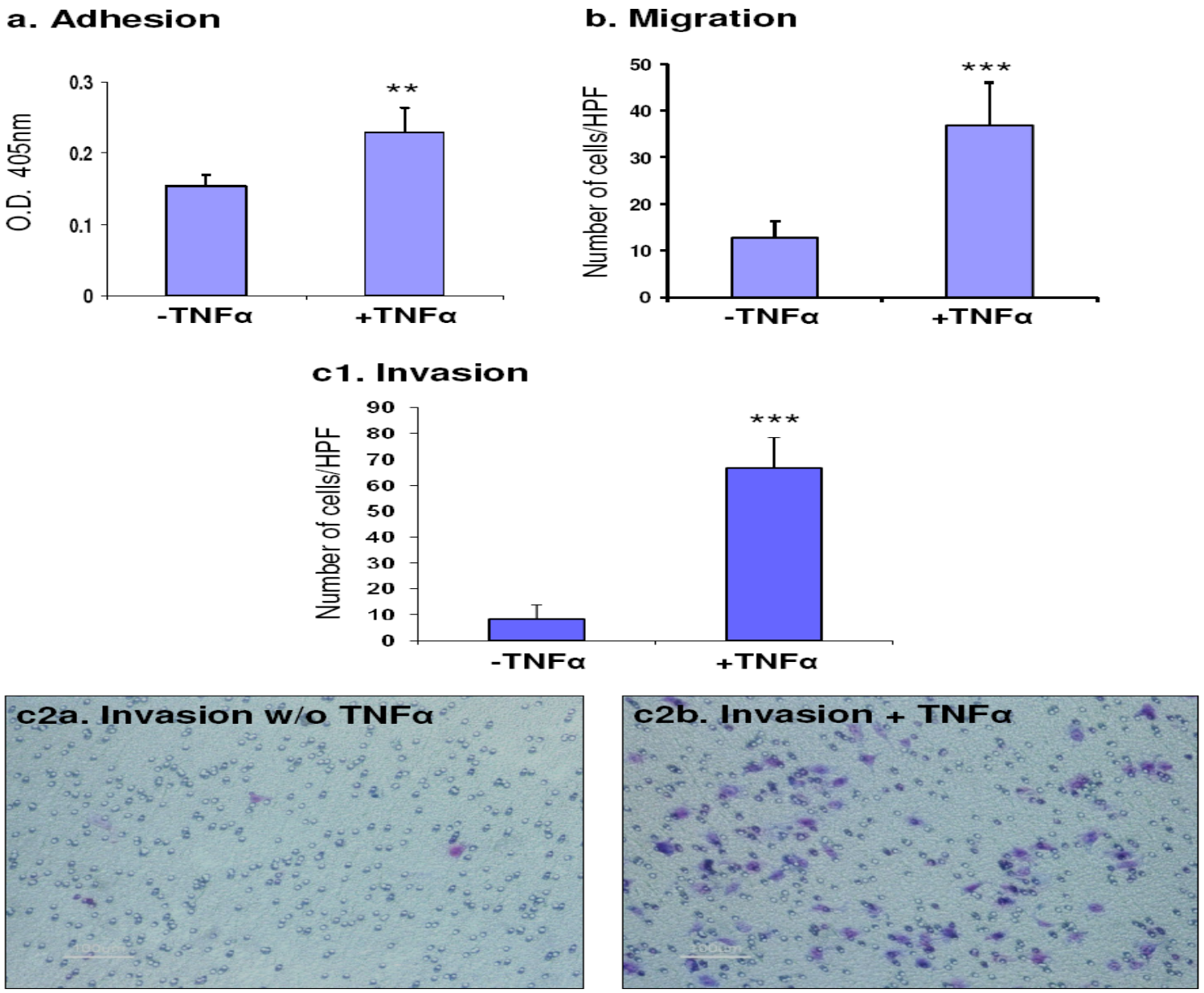
c. Invasive Ductal Carcinoma – No Relapse



d. Invasive Ductal Carcinoma – With Relapse




Benign
DCIS
IDC – No Relapse
IDC – With Relapse
2/38 5.3%
14/30 46.7%
13/23 56.5%
18/35 51.4%
4/38 10.5%
19/30 63.3%
18/23 78.3%
22/35 62.9%
3/38 7.9%
15/30 50.0%
17/23 73.9%
30/35 85.7%
4/38 10.5%
18/30 60.0%
15/23 65.2%
31/35 88.6%
p=0.005
p=0.017
Incidence (% positive)
100
80
60
40
20
0
***
CCL2
CCL5
TNFα
IL-1β


a. Adhesion
O.D. 405nm
0.3
0.2
0.1
0
**
-TNFα
+TNFα
b. Migration
Number of cells/HPF
50
40
30
20
10
0
***
-TNFα
+TNFα
c1. Invasion
Number of cells/HPF
90
80
70
60
50
40
30
20
10
0
***
-TNFα
+TNFα
c2a. Invasion w/o TNFα
c2b. Invasion + TNFα