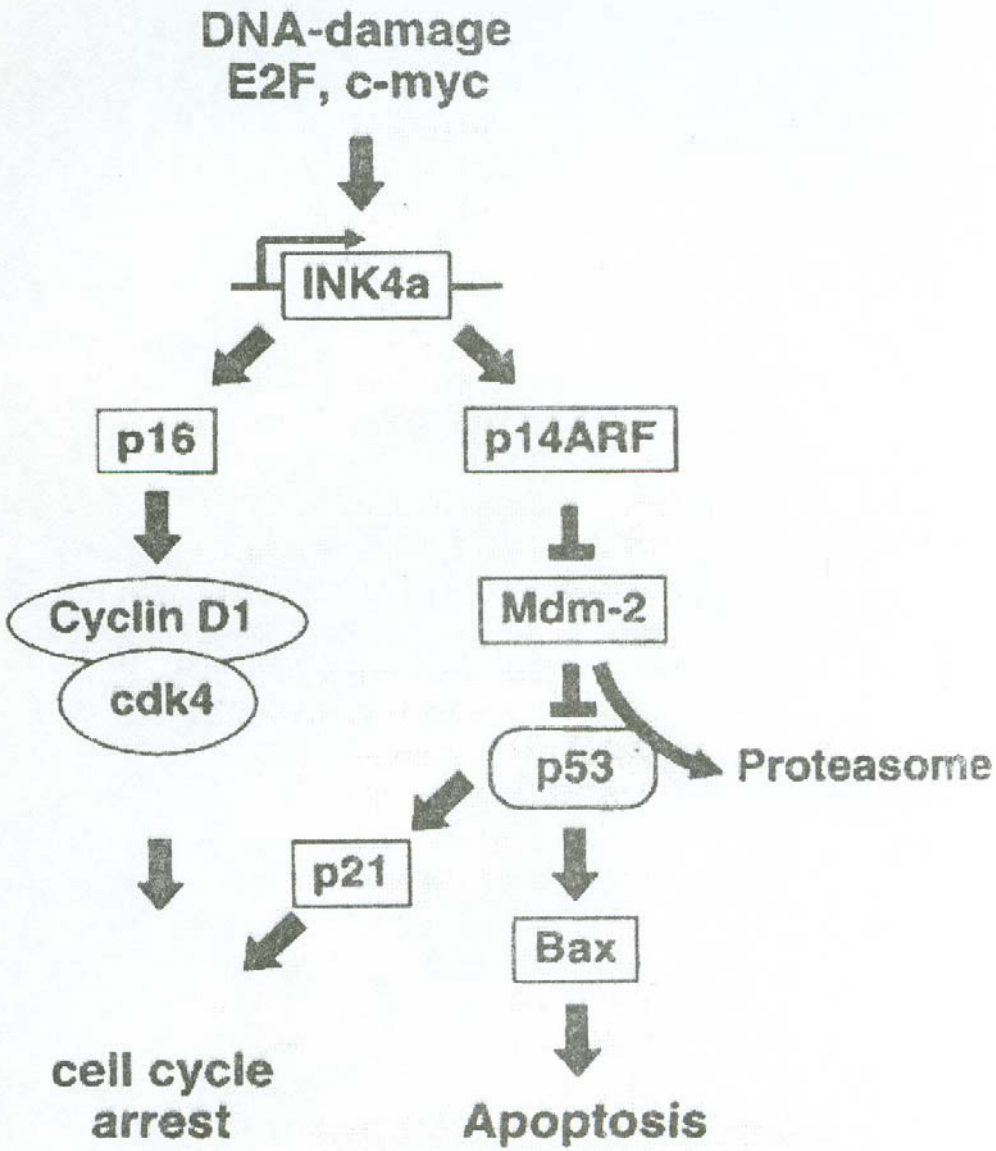
APOPTOSIS Y CICLO CELULAR



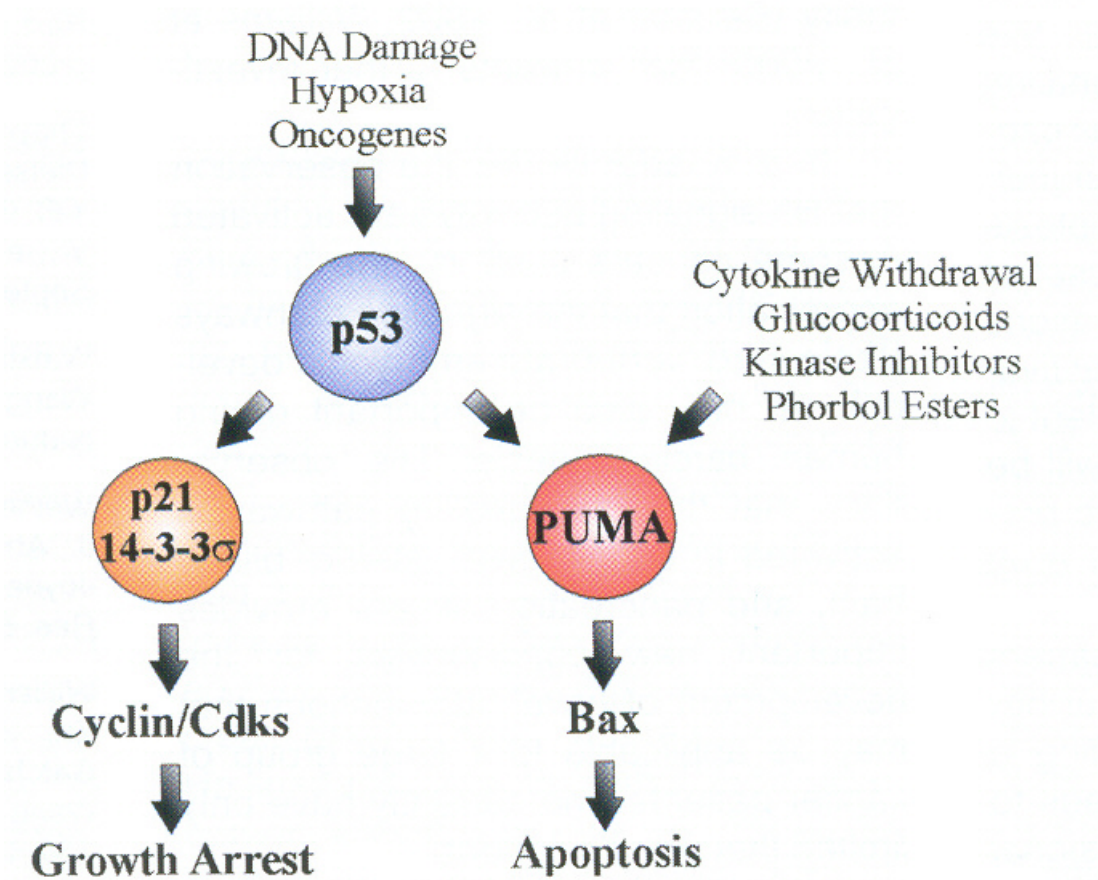
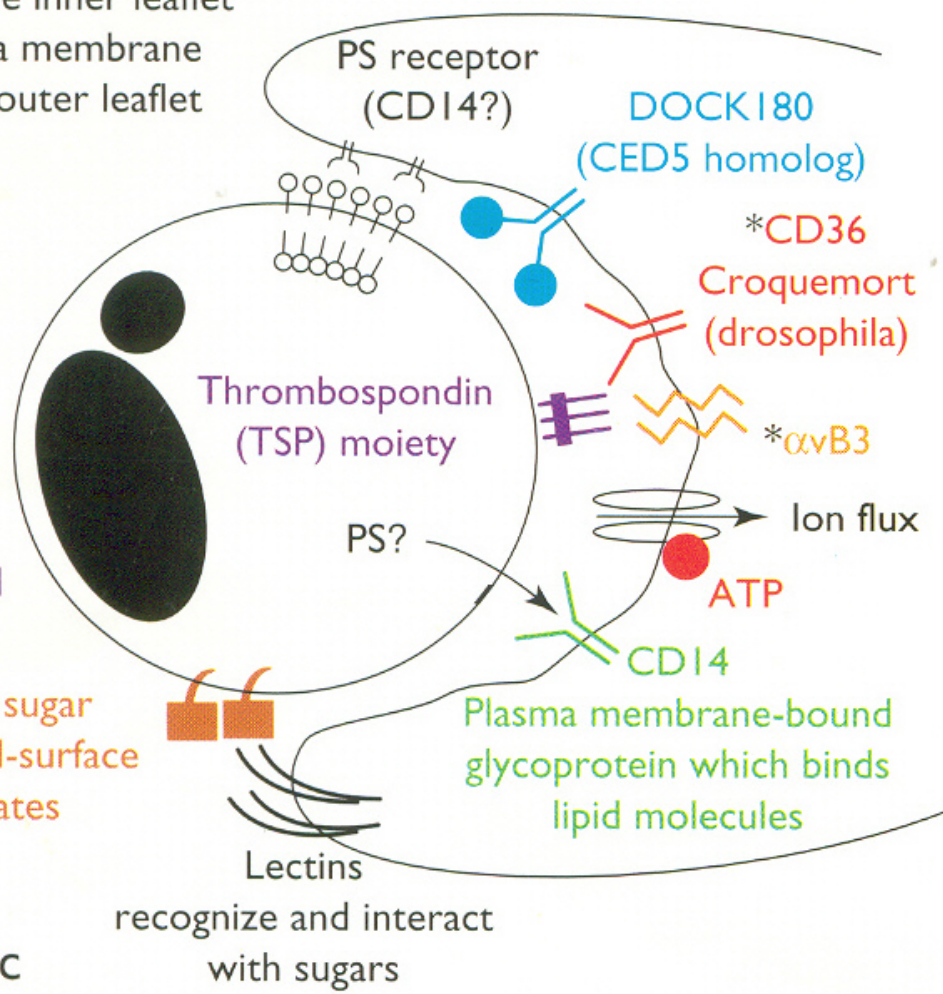


Figure 1. PUMA is essential for p53-dependent and -independent apoptosis

p53 induces either cell cycle arrest or apoptosis depending on cell type and subcellular context. PUMA is required for p53-dependent apoptosis induced by DNA damage, hypoxia, and oncogenes. PUMA is also necessary for apoptosis induced by p53-independent stimuli including serum withdrawal, glucocorticoids, kinase inhibitors, and phorbol esters. p53-dependent cell cycle arrest is mediated by p21 and 14-3-3σ.

Cancer Cell 4, 4, 2003

Phagocytosis



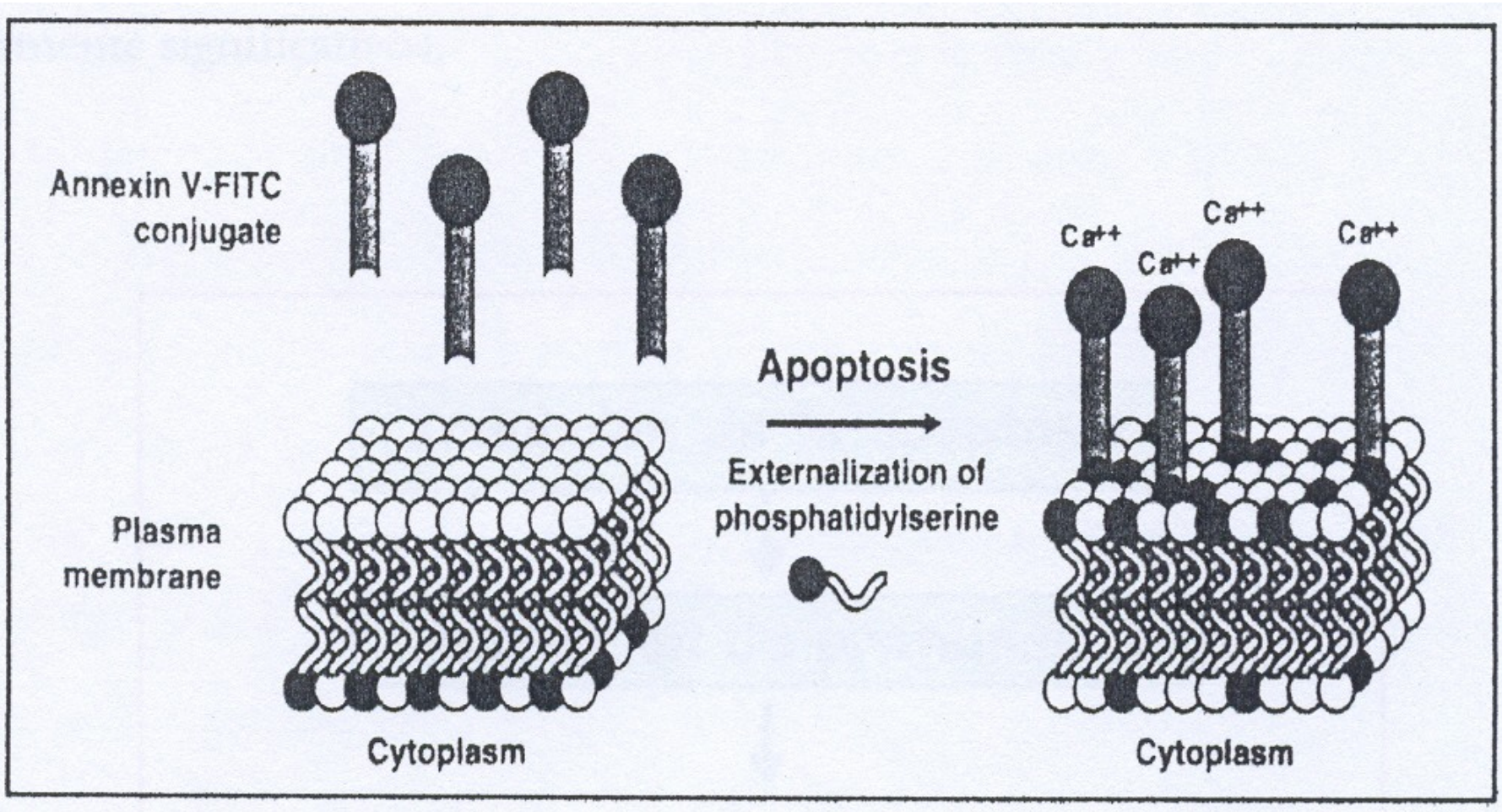
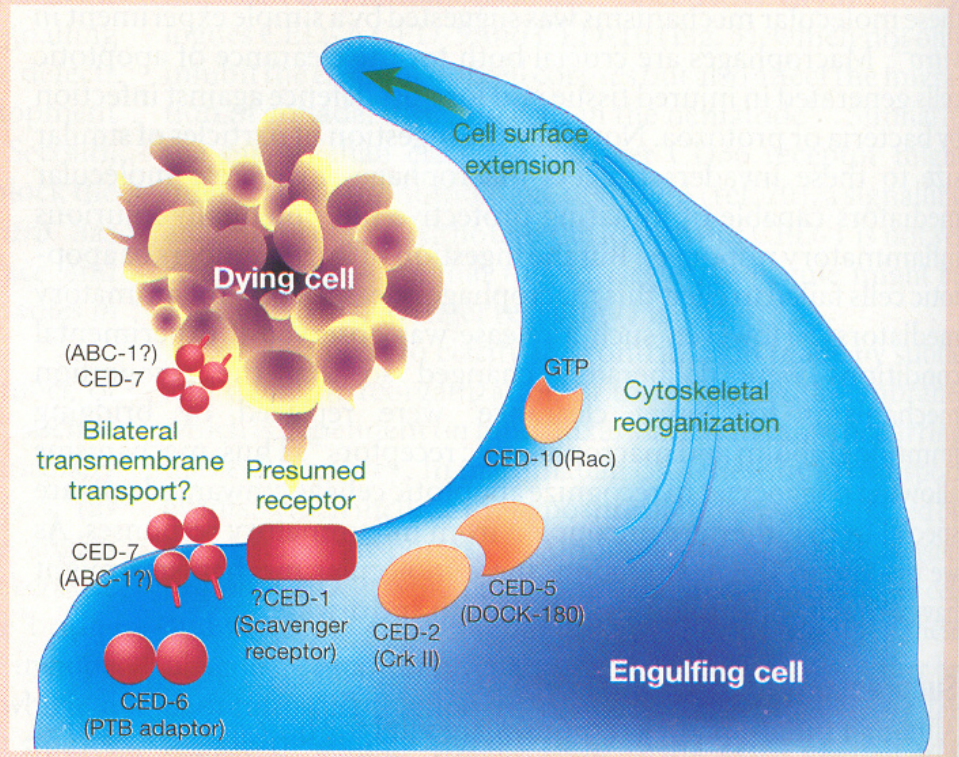

Annexin V-FITC
conjugate
Plasma
membrane
Cytoplasm
Apoptosis
Externalization of
phosphatidylserine
Ca++
Ca++
Ca++
Ca++
Cytoplasm

Figure 3 Signalling the engulfment of dying cells in *Caenorhabditis elegans*. Mutations in six genes are known to affect the engulfment of cell corpses by non-professional neighbouring cells in this nematode. CED-2, CED-5 and CED-10 intracellular proteins signal in a manner comparable to their respective mammalian homologues CrkII, DOCK 180 and Rac, mediating the cytoskeletal reorganization and extension of the engulfing cell surface around the dying cell. CED-7, homologous with mammalian phagocyte ABC-1, acts in both dying and engulfing cells[6], possibly in transmembrane lipid transport. We speculate that CED-1, yet to be characterized, is analogous to mammalian scavenger receptors; CED-7 and CED-1 probably promote engulfment by interacting with the signalling adaptor protein CED-6. PTB, phosphotyrosine binding.



Nature 407,

II, 2000

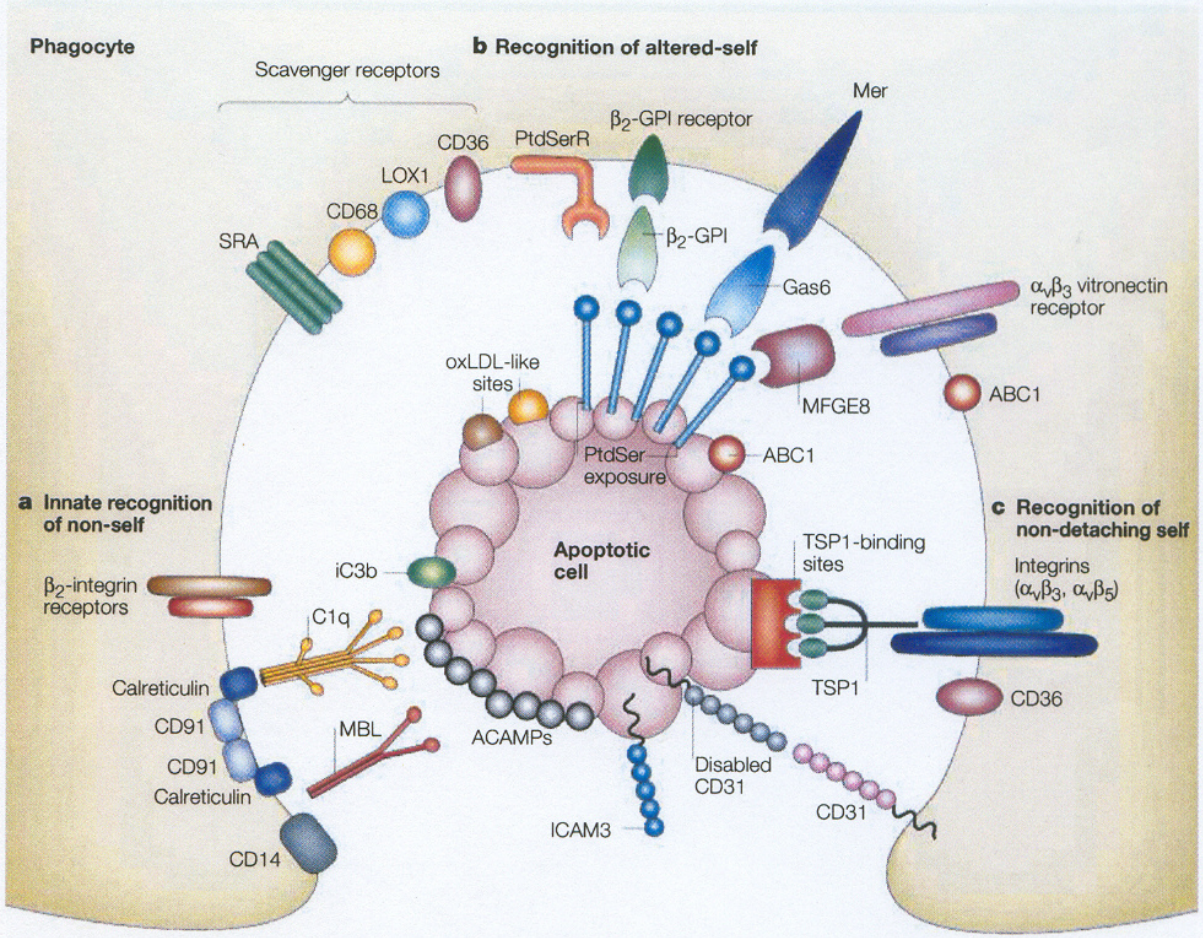


Figure 1 | **Three classes of mechanism for the recognition of apoptotic cells by phagocytes. a** | Innate recognition of non-self involves phagocyte CD14, β_2-integrins (which bind the opsonic complement fragment inactivated C3b, iC3b) and the CD91–calreticulin complex (which can bind the first component of complement, C1q, and mannose-binding lectin, MBL, which recognizes pathogen-like apoptotic-cell-associated molecular patterns, ACAMPs). **b** | Recognition of altered-self involves an array of scavenger receptors, including the class-A scavenger receptor (SRA), CD68, LOX1 (oxidised low-density lipoprotein receptor 1) and CD36, which recognize oxidised sites on apoptotic cells that mimic oxidised low-density lipoprotein (oxLDL). Exposure of phosphatidylserine (PtdSer) on the surface of apoptotic cells is a key 'eat-me' flag. It is detected by phagocyte phosphatidylserine receptor (PtdSerR), receptors for the bridging plasma-protein β_2-glycoprotein I (β_2-GPI), the Mer kinase receptor for the bridging protein Gas6, and $\alpha_v\beta_3$ integrin (vitronectin receptor), which binds the bridging protein milk-fat globule epidermal growth factor 8 (MFGE8). Rearrangement of plasma-membrane lipids in both the dying cell and the phagocyte by the ATP-binding cassette transporter ABC1 can contribute to this type of recognition. **c** | Recognition of non-detaching self involves disabling the detachment signals that are conferred by apoptotic-cell CD31 and, possibly, similar alterations in another immunoglobulin-superfamily member, intercellular adhesion molecule 3 (ICAM3). Disabled apoptotic-cell CD31 binds tightly to phagocyte CD31, which may promote binding of the bridging protein thrombospondin-1 (TSP1) by phagocyte integrins.

Nature Reviews Immunology, 2, 2002

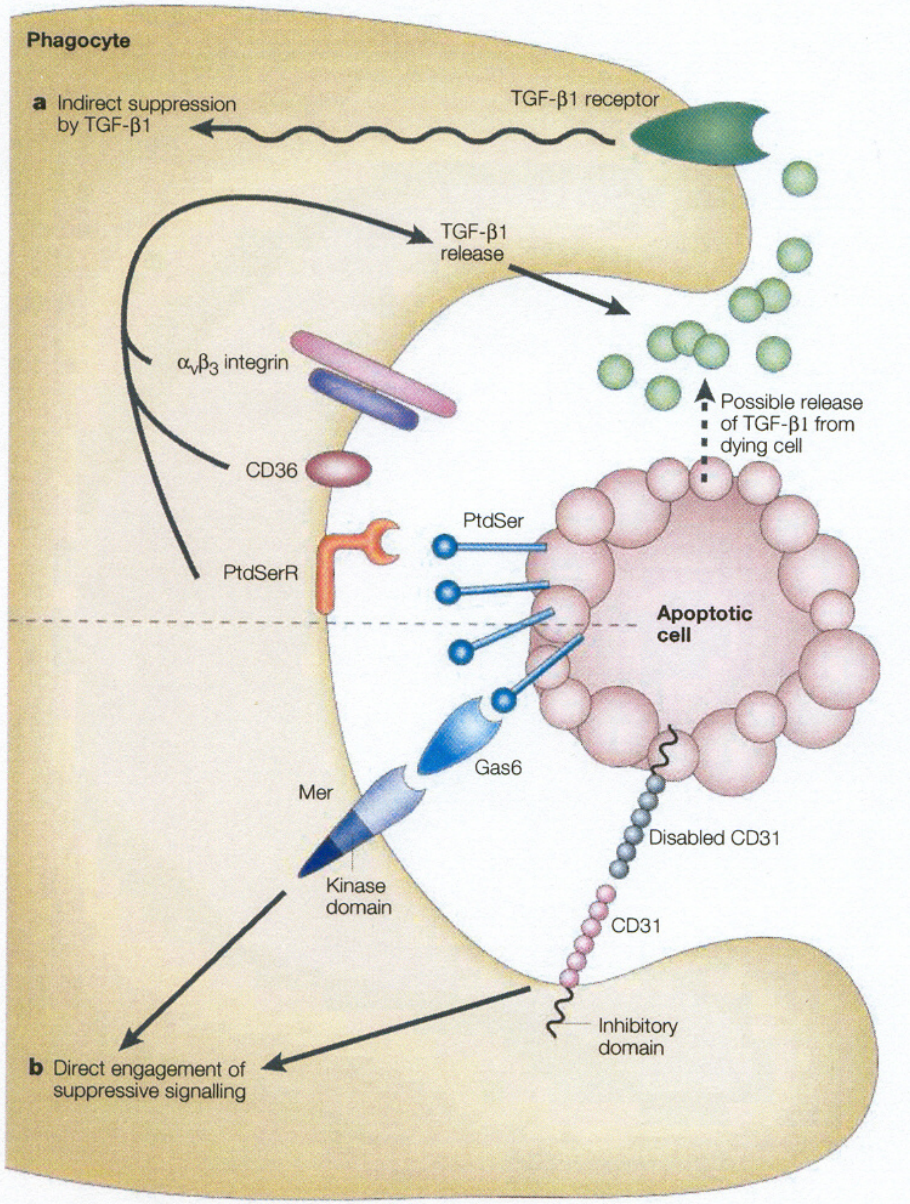
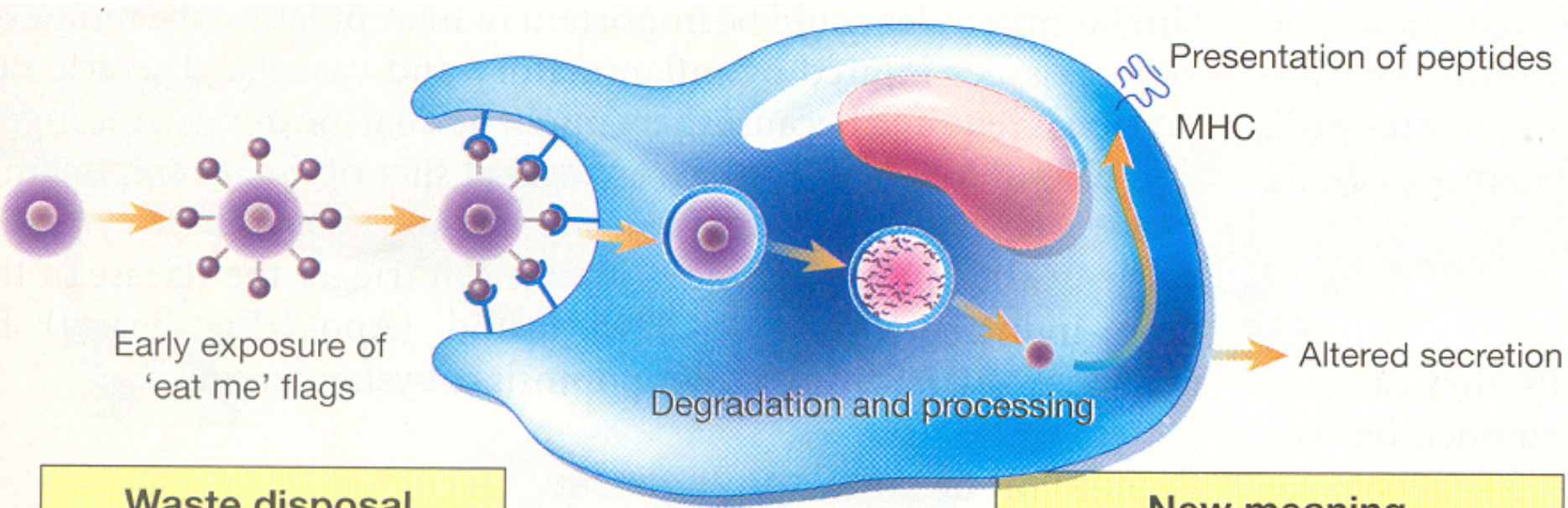


Figure 3 | **Two classes of mechanism for apoptotic-cell suppression of phagocyte pro-inflammatory responses. a** | Indirect suppression by transforming growth factor-β1 (TGF-β1) derived from macrophages that have ingested apoptotic cells is triggered by ligation of the macrophage receptor for phosphatidylserine (PtdSerR), CD36 and $\alpha_v\beta_3$ integrin, possibly supplemented by the direct release of TGF-β1 from dying cells. Similar mechanisms might apply for interleukin-10 (not shown). **b** | Direct suppressive signalling could arise through the kinase domain of Mer and the tyrosine inhibitory domain of CD31 and, possibly, related inhibitory receptors.

Nature Reviews Immunology, 2, 2002



Waste disposal

- Removal of cell corpses
- Prevention of leakage of contents from dying cells

New meaning

- Suppression of inflammation (TGF-β1↑, PGE_2↑, TNF-α↓)
- Modulation of cell killing (NO↓, CD95L↑)
- Regulation of immune response (via class I and II MHC)

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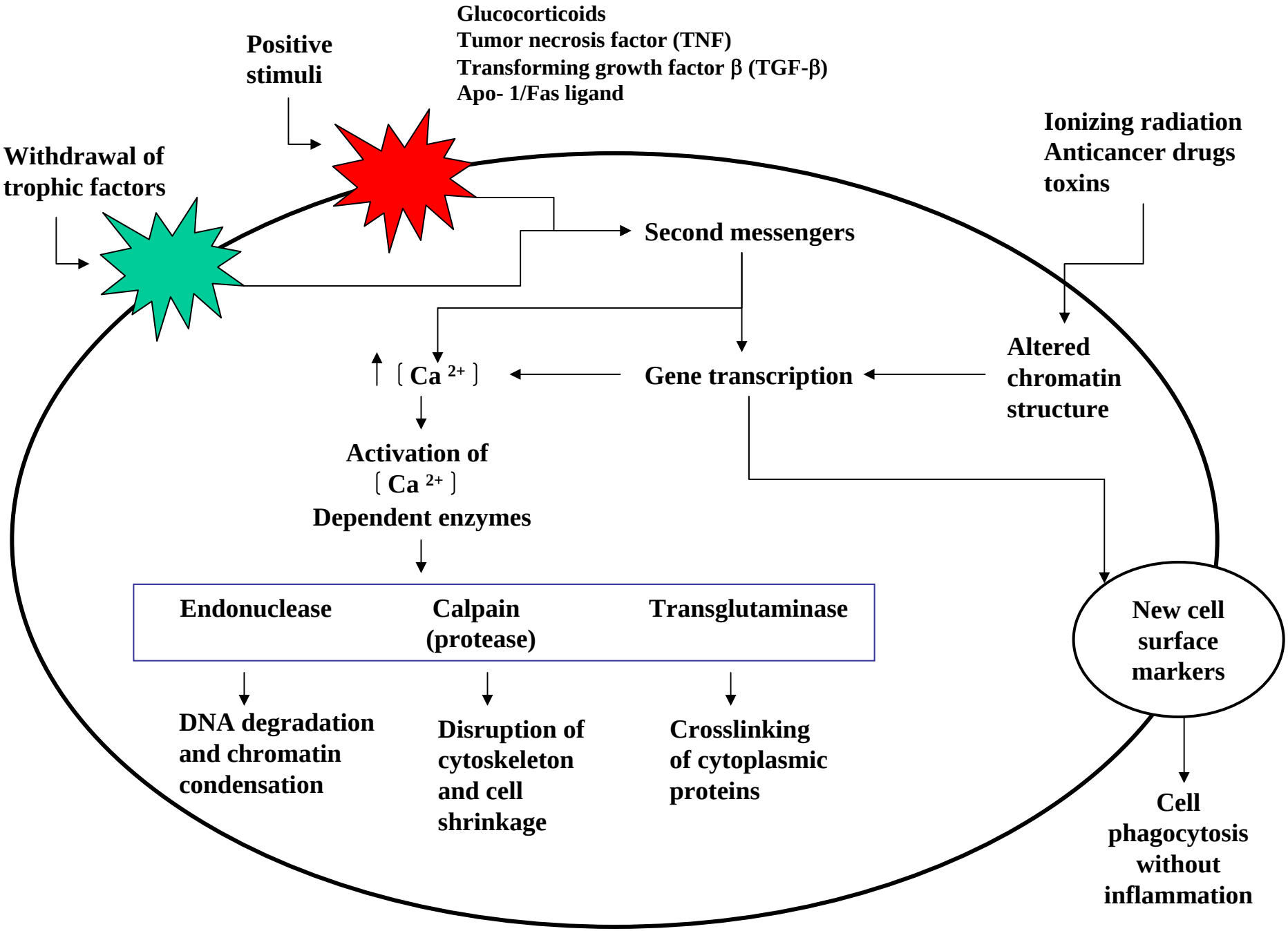
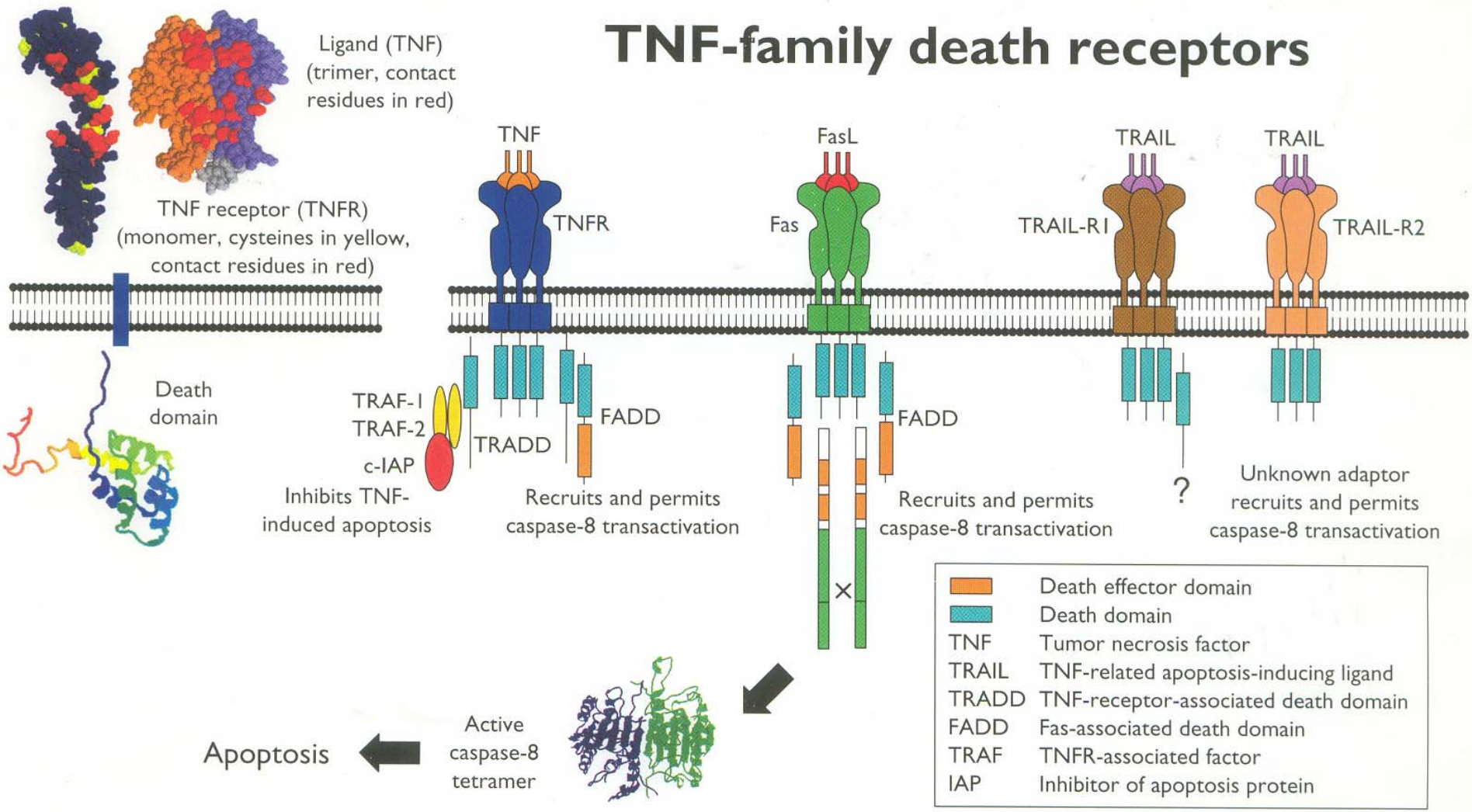


Fig-1 Common metabolic events in apoptosis

TNF-family death receptors



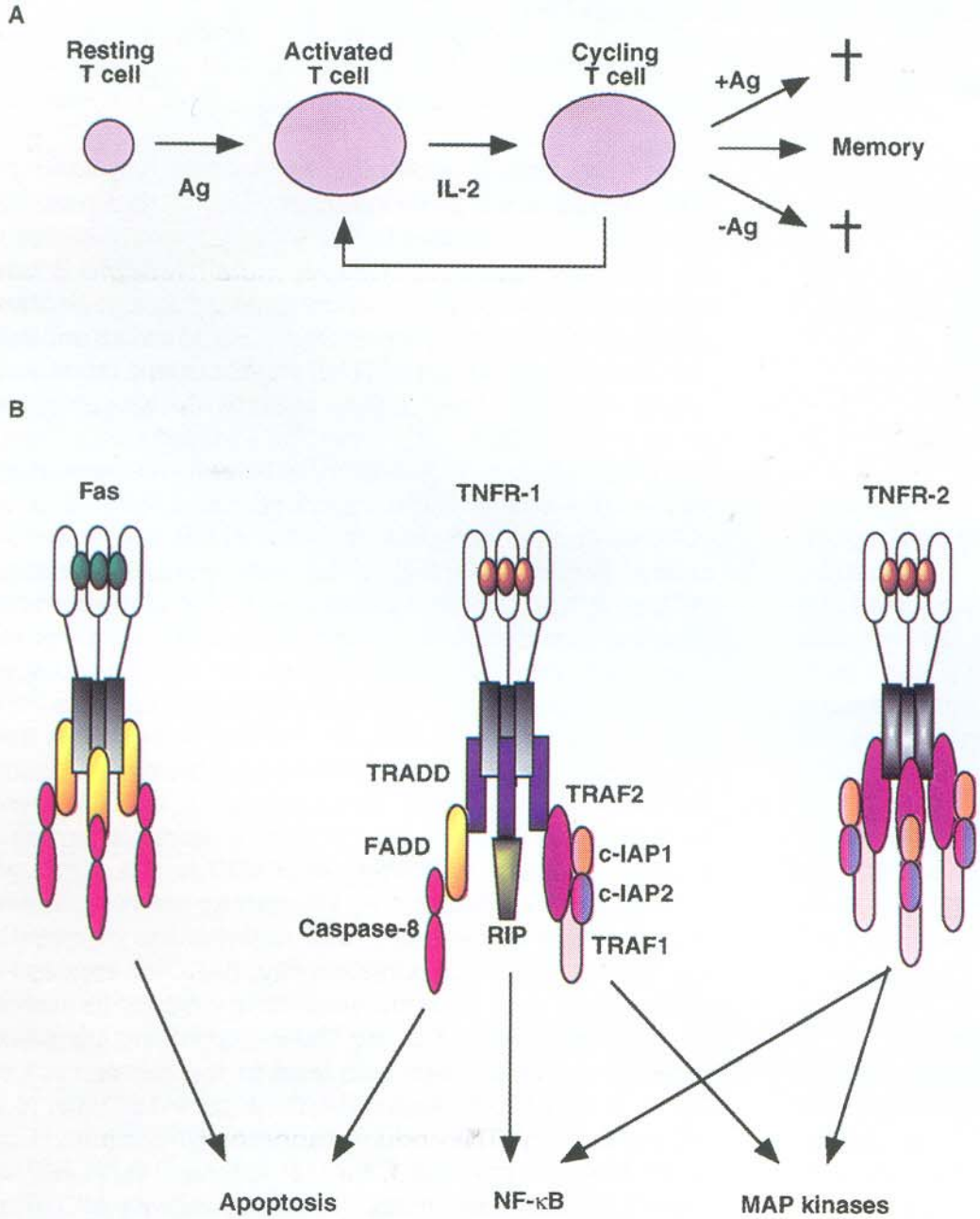


Figure 1. TNFR Signaling and T Cell Homeostasis

(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.

Immunity, 1, 2000,

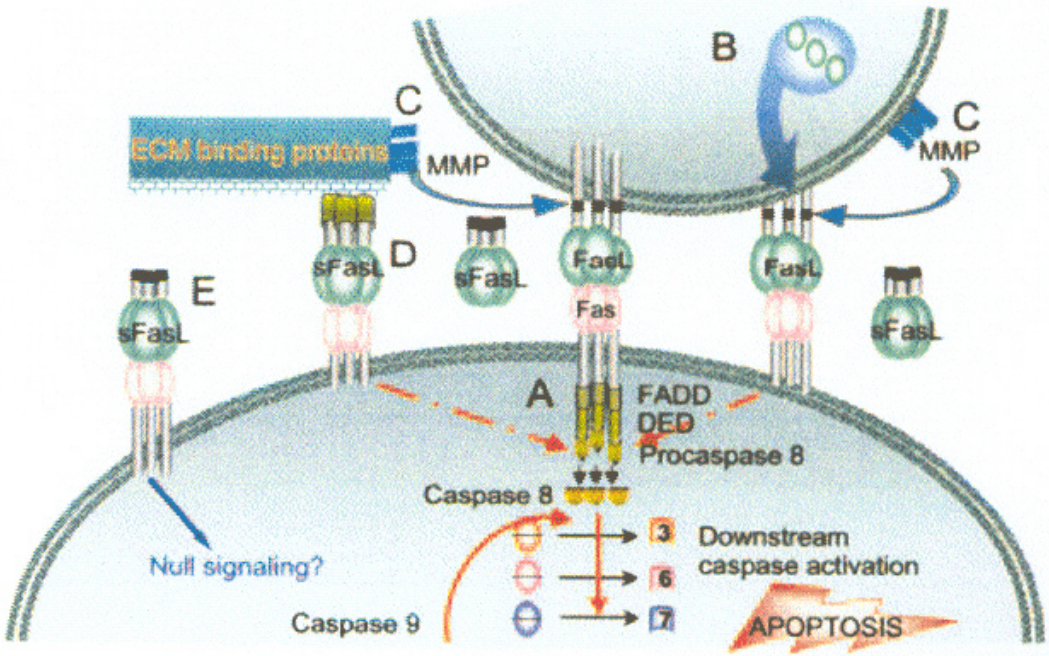
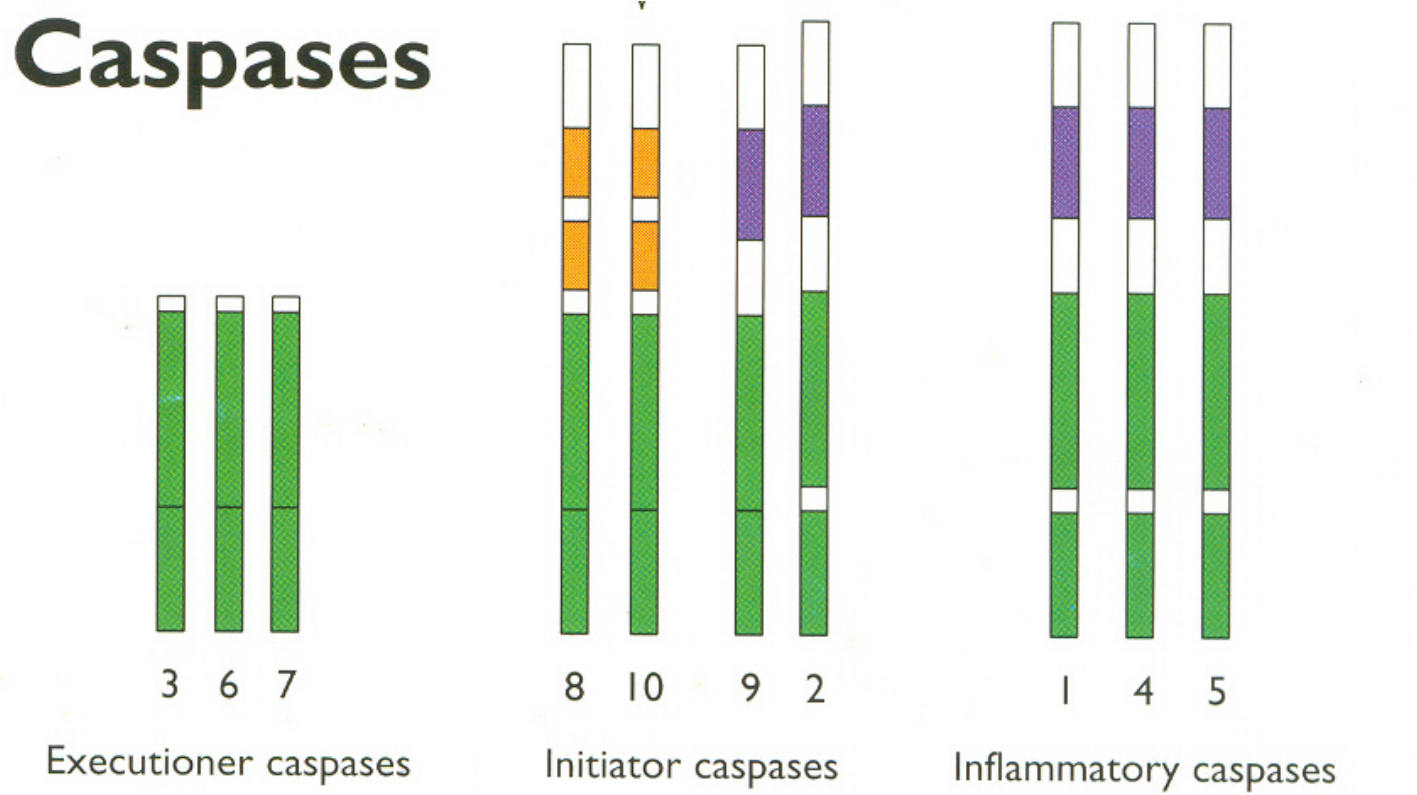
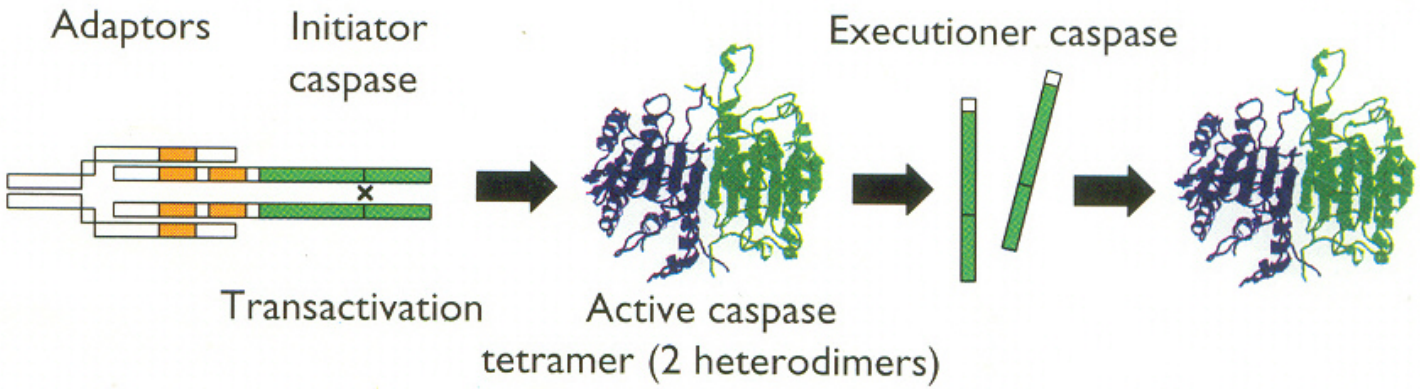


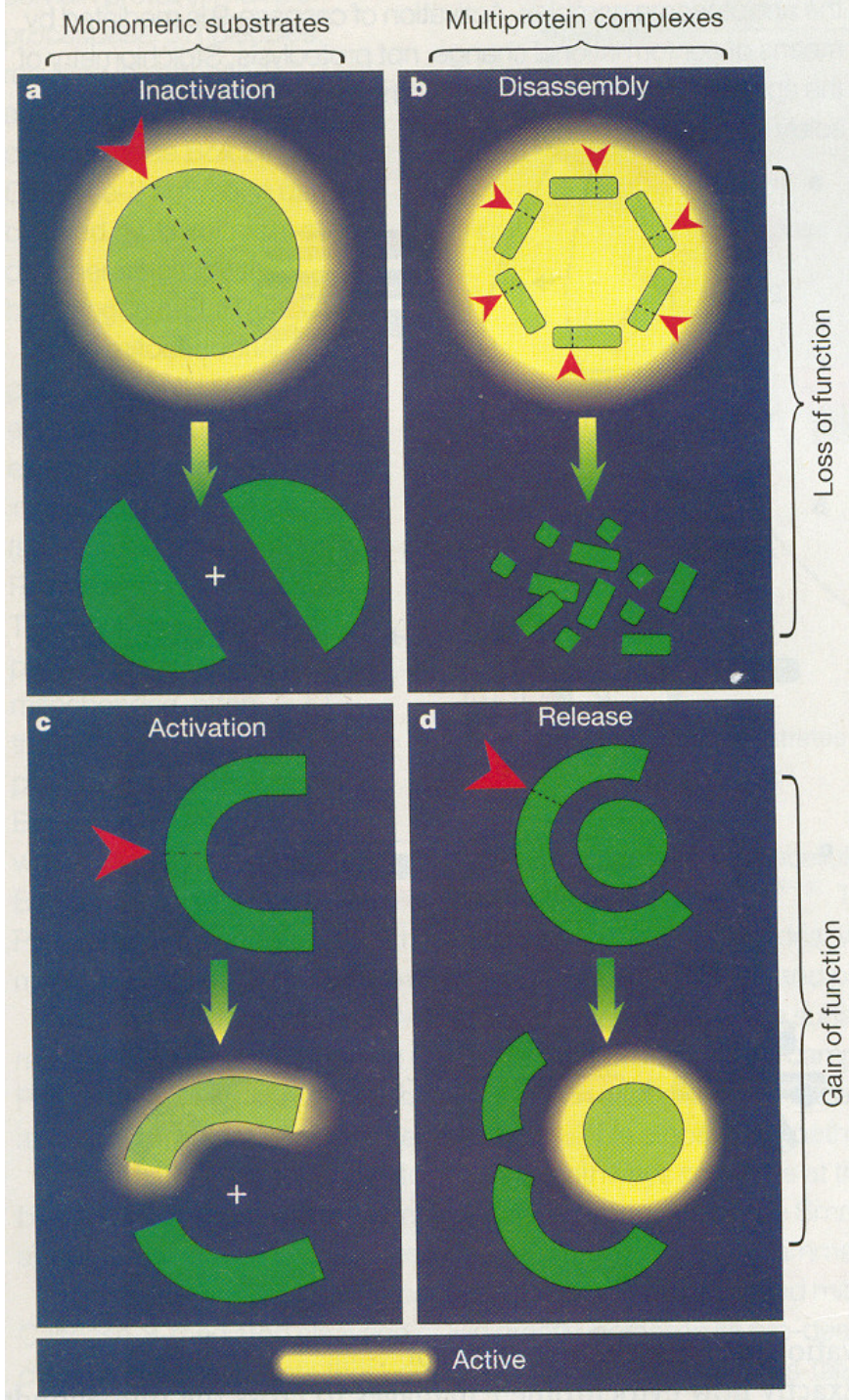
Figure 2. Fas/FasL-mediated apoptosis. (A) Binding of 3 FasL molecules with Fas leads to cell surface oligomerization, recruitment of the adapter protein FADD (Fas-associated protein with death domain), and procaspase-8 via its death effector domain (DED) into a death-inducing signaling complex (DISC). Activation of procaspase-8 by autocatalysis results in the initiation of extrinsic apoptosis by converting inactive effector procaspases-3, -6, and -7 into active enzymes via transproteolysis and intrinsic apoptosis via cleavage of Bid, release of cytochrome c, and activation of caspase-9 (not shown). (B) FasL is synthesized and stored as a membranous protein in vesicles by selected cell types. Upon activation by various physiologic stimuli, these vesicles are excreted from the cell and cause apoptosis of Fas-positive cells. (C) Wild-type FasL is cleaved from the cell surface by matrix metalloproteinases (MMPs) and accumulates as a soluble protein (sFasL). (D) sFasL may transiently interact with proteins on the cell surface or the extracellular matrix (ECM) to form oligomeric structures with apoptotic activity. (E) sFasL as a soluble homotrimer cannot induce oligomerization of Fas and as such blocks apoptosis by competing with the membranous form for Fas binding.

Blood, 105 (4), 2005

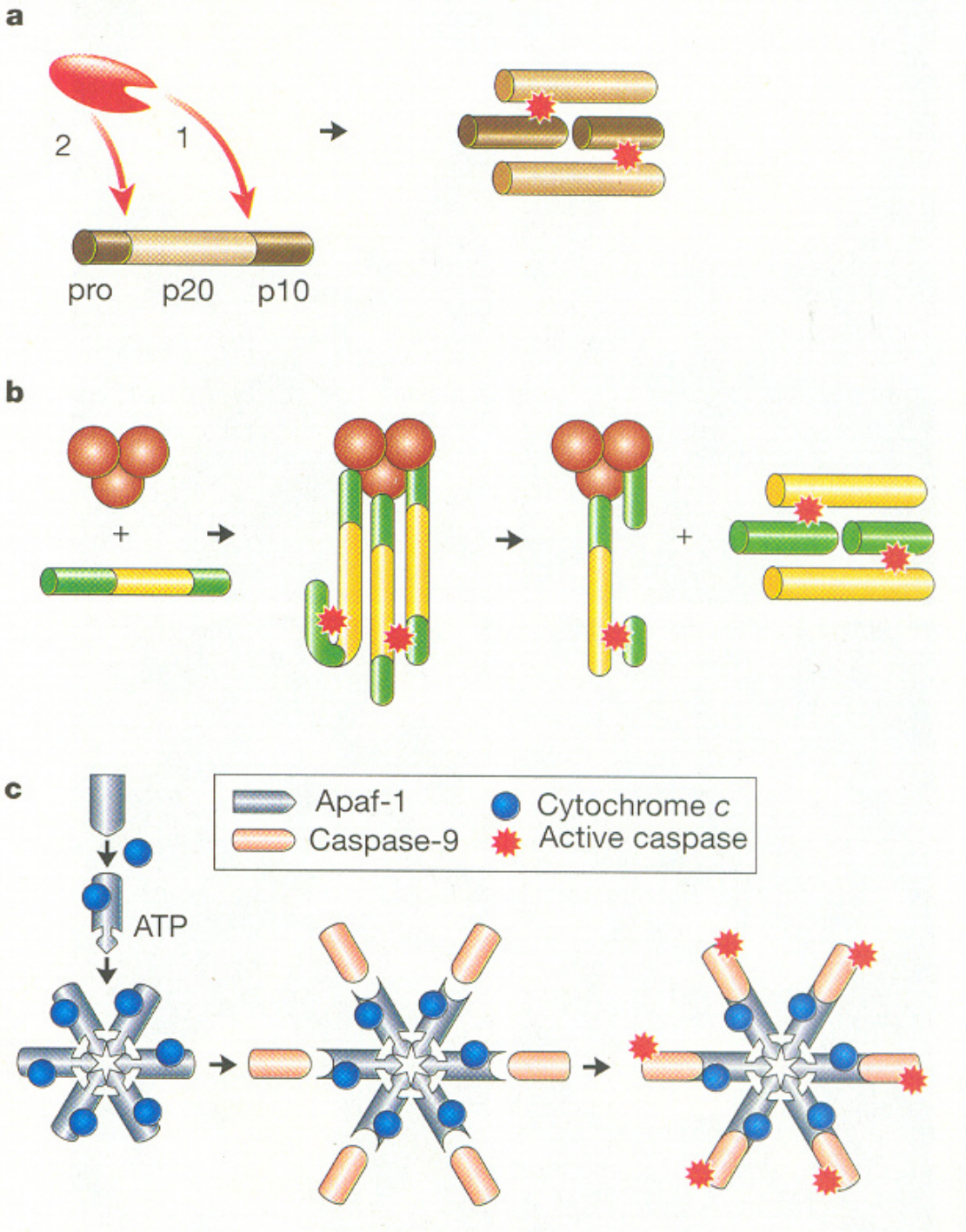
Caspases


3 6 7
Executioner caspases
8 10 9 2
Initiator caspases
1 4 5
Inflammatory caspases
Death effector domain
Caspase recruitment domain
Prodomain
Protease subunits


Adaptors
Initiator caspase
Executioner caspase
Transactivation
Active caspase tetramer (2 heterodimers)

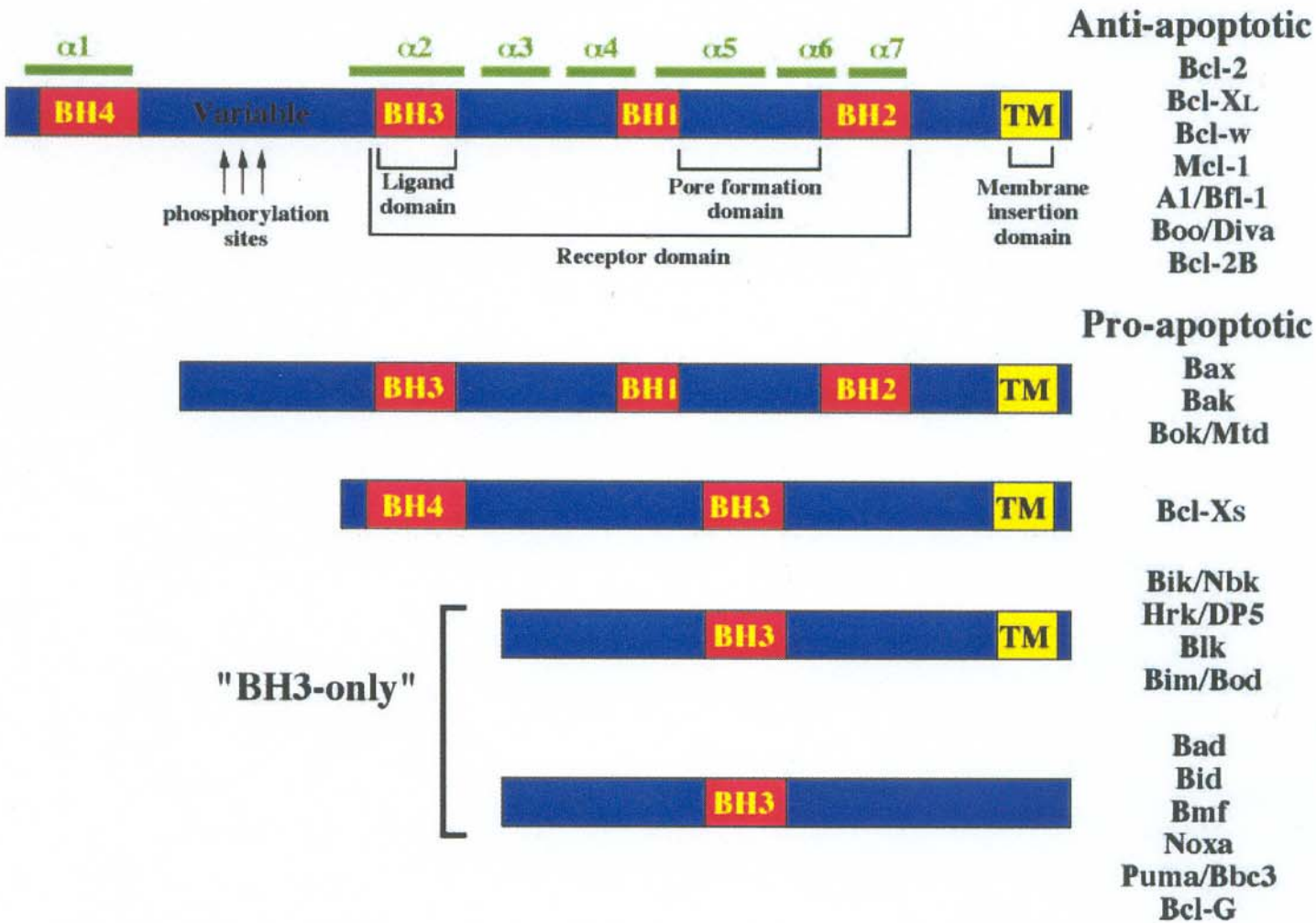


Nature 407, II, 2000



Nature 407, II, 2000

Box 1 Proteins from the Bcl-2 family. Proteins from the Bcl-2 family share homology with Bcl-2 in the Bcl-2 homology regions (BH1 to BH4). Two classes of Bcl-2 family members can be distinguished. Anti-apoptotic Bcl-2 homologs possess all four BH1 homology regions. These proteins are primarily localized in mitochondria and stabilize their membranes. Pro-apoptotic Bcl-2 homologs can lack the BH4 domain (Bax, Bak, Bok/Mtd), BH2 (Bcl-XS), or BH1, BH2, and BH4. These latter proteins are referred to as 'BH-3-only' proteins and can possess a C-terminal transmembrane (TM) region.



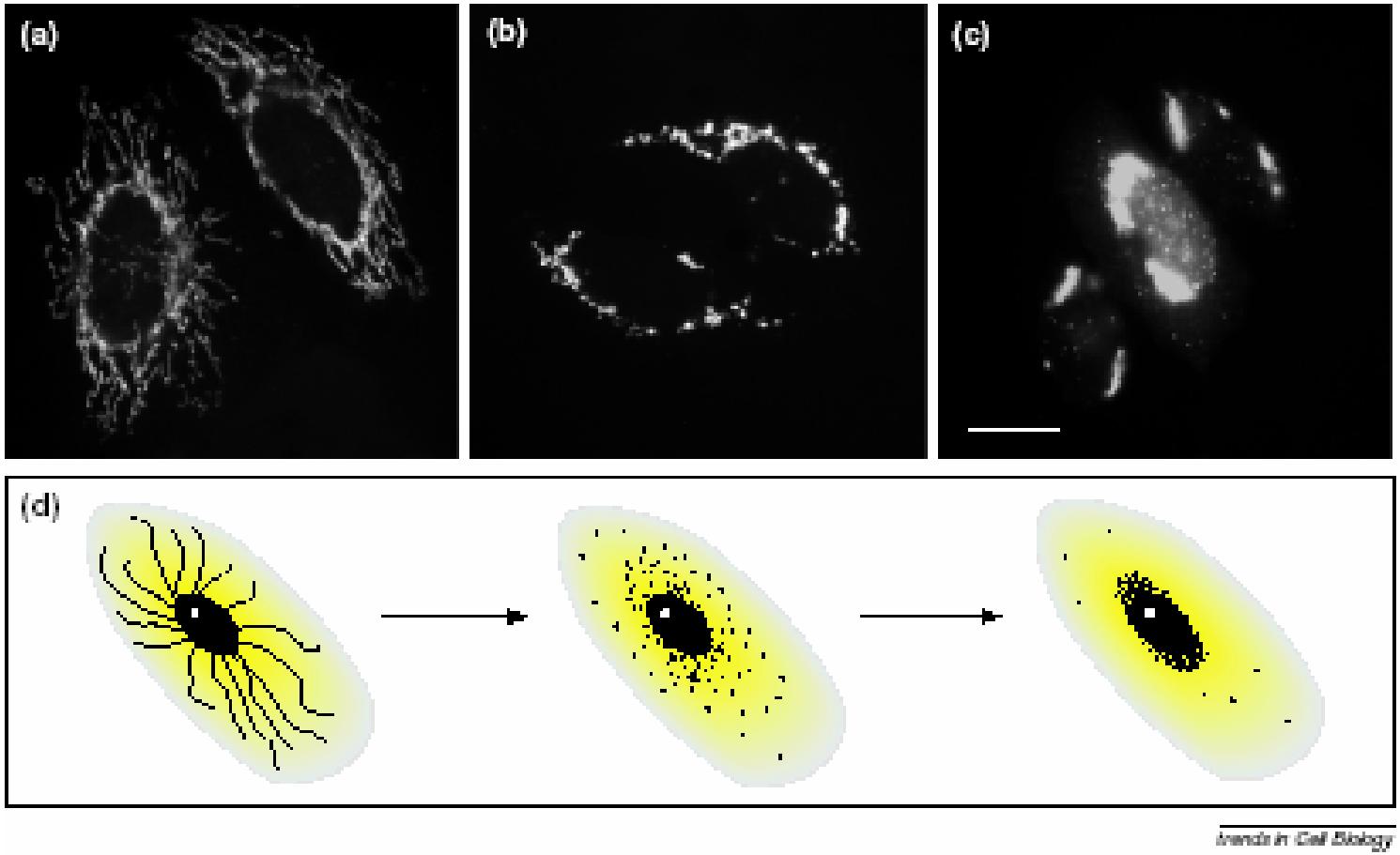


FIGURE 1

Morphological changes and redistribution of mitochondria in HeLa cells overexpressing Bax. (a) Control HeLa cells immunostained with an antibody against mitochondrial Hsp70 in order to reveal mitochondria. (b,c) Mitochondria from HeLa cells labelled with the same antibody, 15 h after transfection with a Bax-encoding cDNA in the presence of the peptide caspase inhibitor z-VAD to prevent apoptosis. Normal cells display 'worm-like' mitochondria (a), but cells overexpressing Bax (assessed by Bax immunostaining, not shown) display either punctiform mitochondria dispersed throughout the cell (b) or mitochondria that have disappeared from the cell periphery to form aggregates around the nucleus (c). These changes are independent of caspase activity. (d) A likely explanation for this is that, following Bax insertion into the outer mitochondrial membrane, mitochondria first condense ('pyknotic mitochondria'), possibly fragment, and then cluster around the nucleus. The condensed mitochondria have lost their cytochrome c (A. Ossen-Sand and J-C. Martinou, unpublished.) Bar, 15 μm.

Trends in Cell Biology, 10, 2000