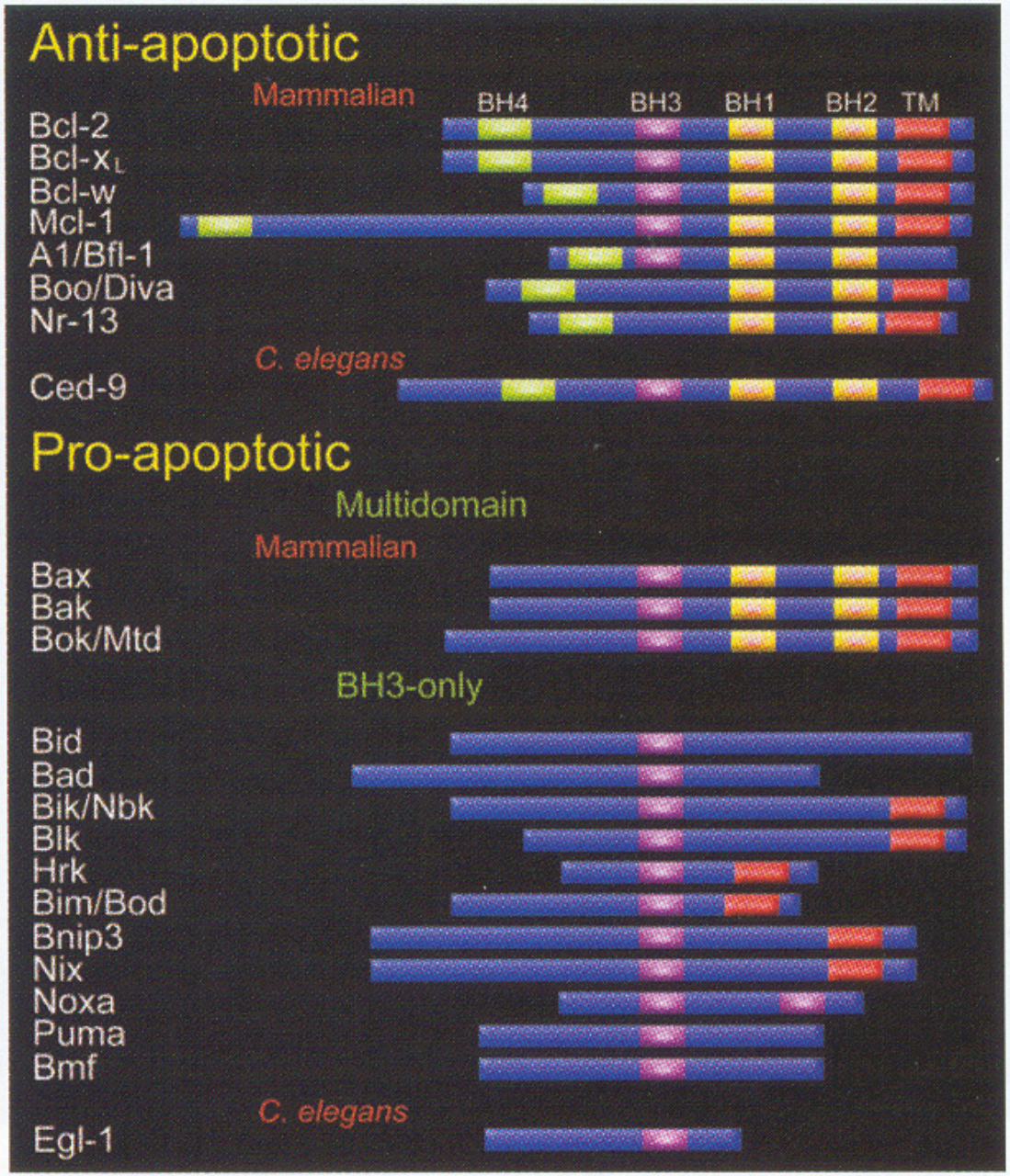

Figure 1. The Bcl-2 family.

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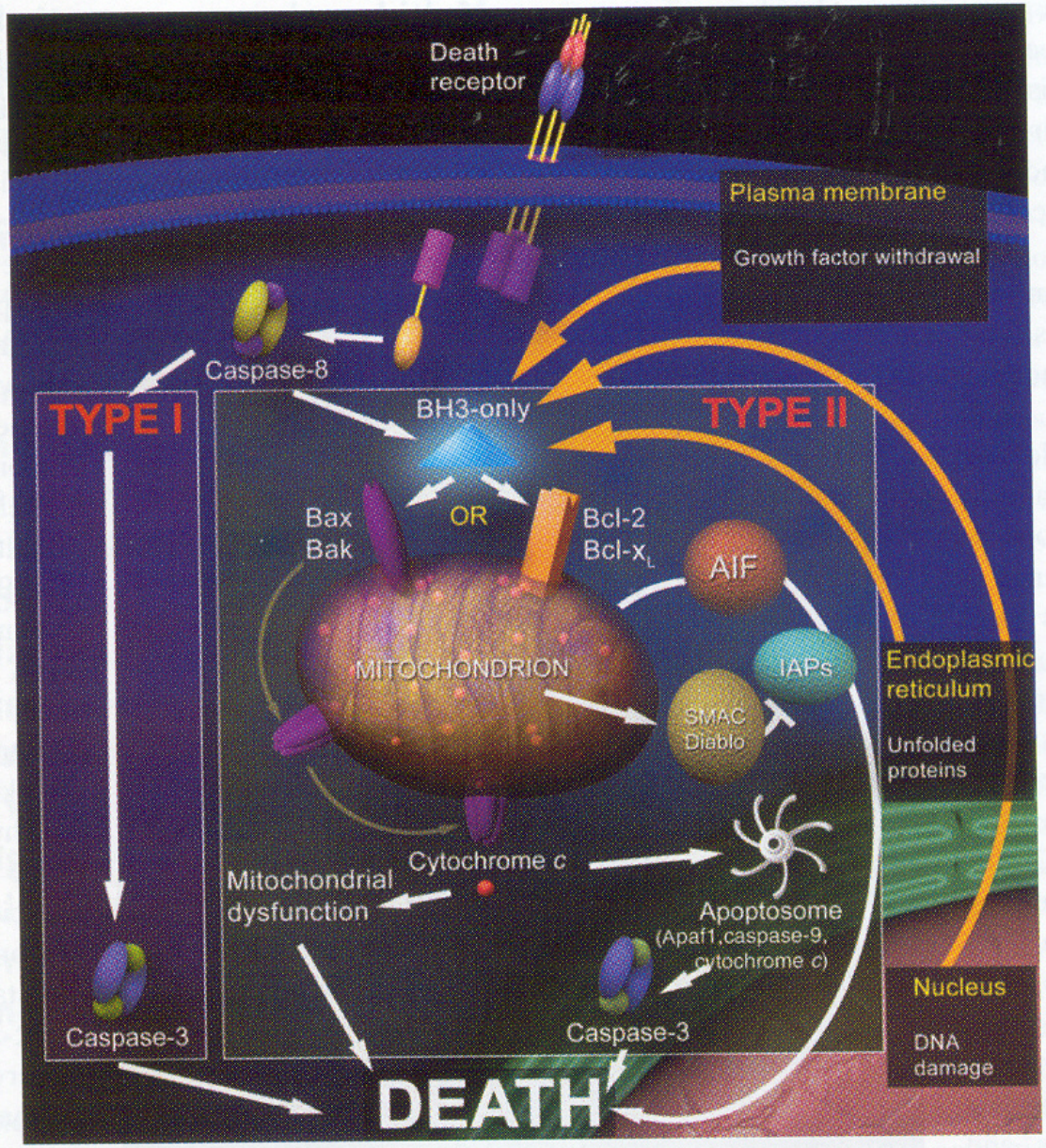

Figure 2. Cell death pathways. Two principal apoptotic execution programs follow death receptor signals: the caspase pathway and mitochondrial dysfunction. Whether a cell will live or die is determined by a balance of positive *versus* negative regulators from the proximal death signals to the core apoptotic pathway.

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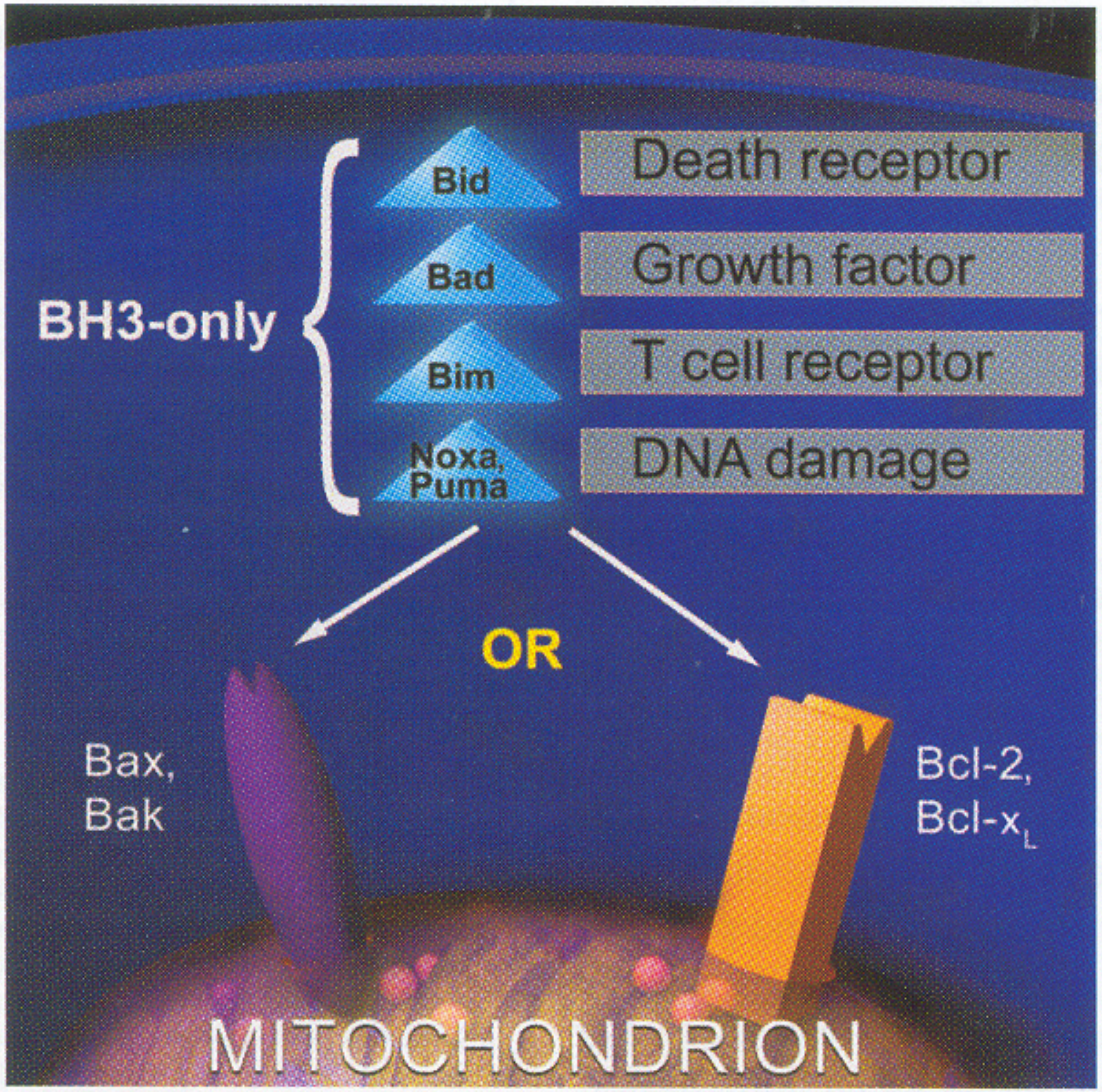

Figure 3. Detail of the mitochondrial apoptotic pathway. The BH3-only molecules Noxa, Puma, Bid, Bim and Bad all activate and require the multidomain pro-apoptotic proteins Bax and Bak to release cytochrome *c* and kill cells. In contrast, anti-apoptotic Bcl-2 or BCL-x_L sequesters BH3-only molecules and blocks the proapoptotic cascade.

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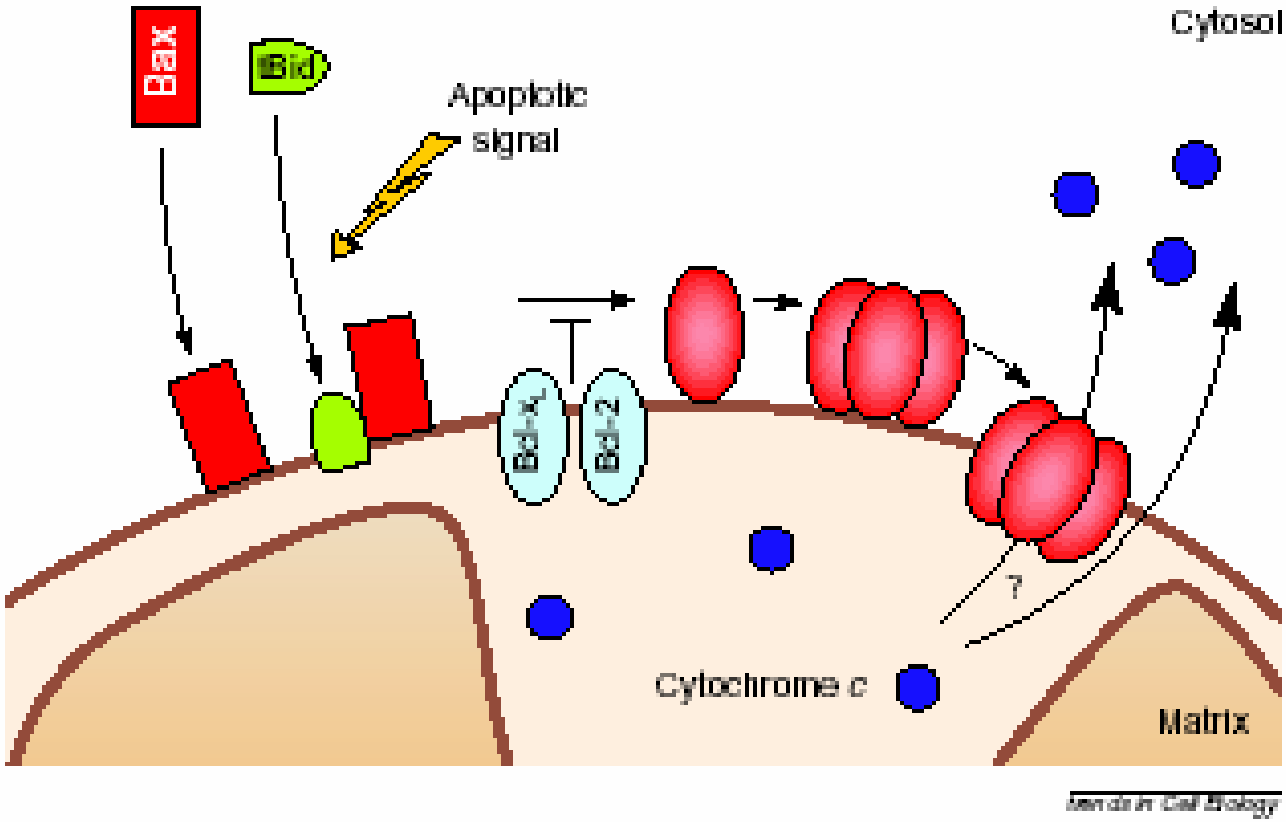

Trends in Cell Biology

FIGURE 3

After an apoptotic signal, Bax moves from the cytosol to the mitochondria. In some cell types, Bax is already loosely attached to the organelles and this translocation cannot be detected. After this, Bax undergoes a conformational change, oligomerizes and inserts into the outer mitochondrial membrane. This is rapidly followed by cytochrome-c release. It is possible that Bax inserts into the membrane before it oligomerizes. All these events can be induced by either full-length Bid or caspase-8-cleaved Bid (tBid) and prevented by Bcl-2 or Bcl-x_L, probably by direct interaction with Bax[33,37]. Another Bax-like protein, Bak, is activated through similar mechanisms[33,78].

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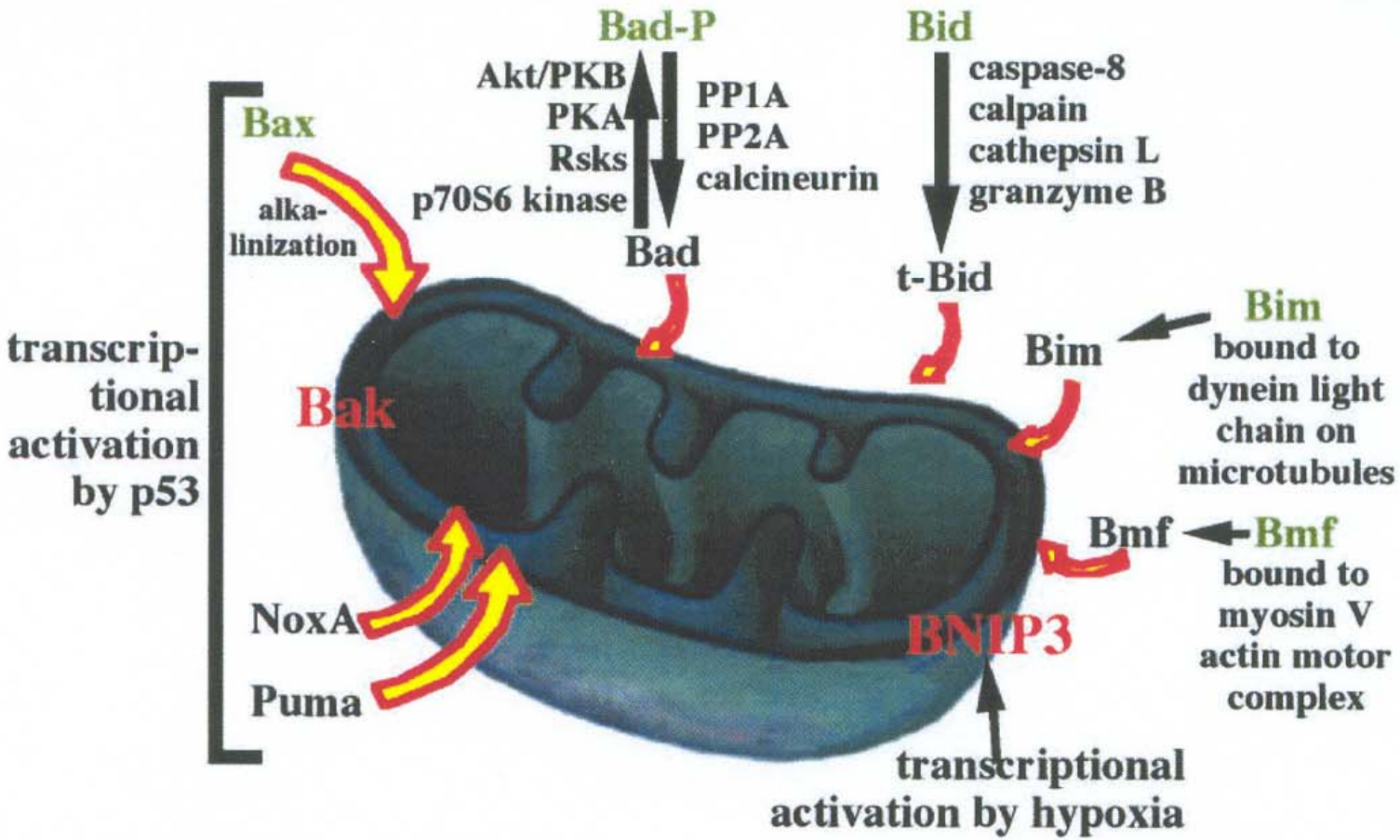
During apoptosis induction pro-apoptotic Bcl-2 family members can translocate from an extra-mitochondrial to mitochondrial membranes, causing their permeabilization. This applies to Bax, which translocates from the cytosol to mitochondria as a result of cytosolic alkalinization. Bid is also normally found in the cytosol and translocates to mitochondria upon digestion by proteases (in particular by caspase-8 but also by calpain, cathepsin L, or granzyme B), yielding truncated Bid (t-Bid). Similar translocation reactions have been described for Bad (which is cytosolic when phosphorylated, for instance by the pro-survival kinase Akt/PKB or other kinases and mitochondrial when dephosphorylated), Bim (which is normally associated with the dynein light chain and hence associated with microtubuli), Bmf (normally associated with the myosin V actin motor complex), as well as NoxA and PUMA (all transcriptionally activated by p53, as Bax). Bak and BNIP3 (which is induced by hypoxia) are constitutively present in mitochondrial membranes.



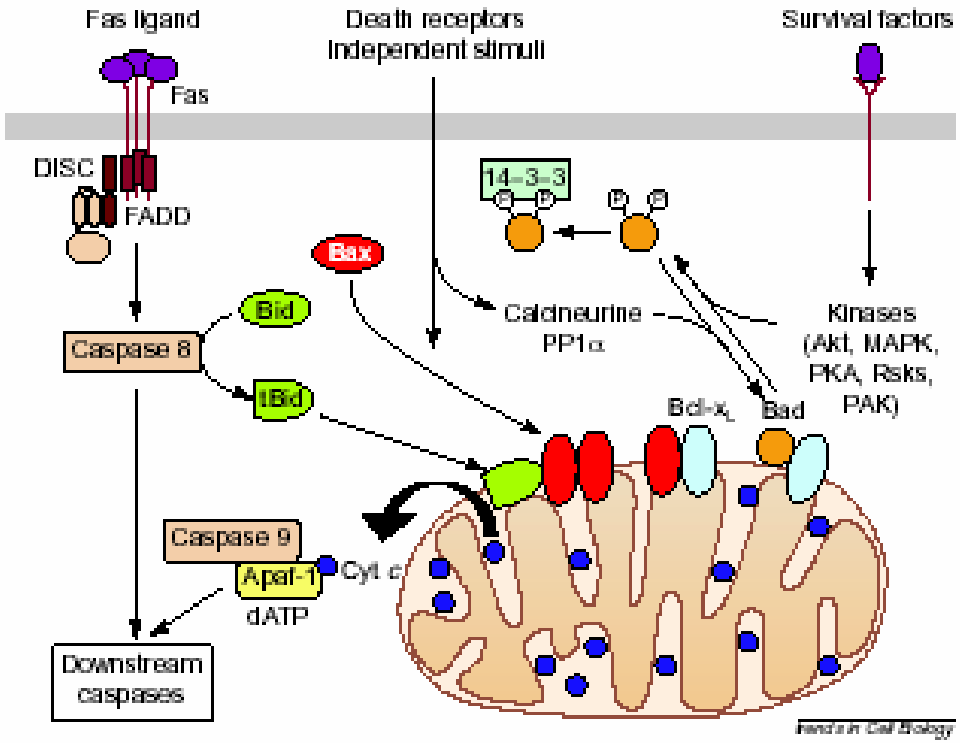


FIGURE 2

Many death signals converge onto mitochondria and are mediated through members of the Bcl-2 protein family called 'BH3-only' proteins, such as Bid and Bad. These proteins are recruited to specific pathways. In some cells, binding of Fas ligand to its receptor Fas leads to the trimerization of Fas and to the formation of the death-inducing signalling complex (DISC). This complex is formed by association of the cytoplasmic region of Fas, the adaptor protein FADD (Fas-associating protein with death domain) and procaspase 8, which is proteolytically cleaved to generate the active enzyme[2]. Caspase 8 then cleaves Bid, whose C-terminal fragment (tBid) translocates to mitochondria, where it activates Bax or Bax-like proteins and results in cytochrome-c (cyt c) release. tBid might also act on its own to trigger cytochrome-c release. Once in the cytosol, cytochrome c activates caspase 9 by binding to Apaf-1 and dATP. The physiological relevance of this pathway has recently been shown by the resistance of Bid-deficient mice to Fas hepatotoxicity[69]. Caspase 8 can also initiate a direct signalling pathway that is independent of mitochondria by cleaving and activating downstream caspases. Death-receptor-independent stimuli and growth-factor deprivation can trigger apoptosis by inducing translocation of Bax or Bad to mitochondria. In healthy cells, Bad can be phosphorylated in response to survival factors by several kinases, including Akt, mitogen-activated protein kinase (MAPK), Erk, protein kinase A (PKA), Rsks (MAPK-activated kinases) and p21-activated kinase 1 (PAK). The two serine residues that are phosphorylated are embedded in a 14–3–3 consensus site. Phosphorylation of either residue or both results in the sequestration of Bad in the cytosol through its binding to 14–3–3. During apoptosis, Bad is dephosphorylated by the Ca^{2+}-sensitive phosphatase calcineurin or the protein phosphatase 1α (PP1α) and translocates to mitochondria, where it binds to Bcl-x_L. This displaces Bcl-x_L from Bcl-x_L–Bax heterodimers, thereby inhibiting the death-repressor activity of Bcl-x_L.

Trends in Cell Biology, 10, 2000

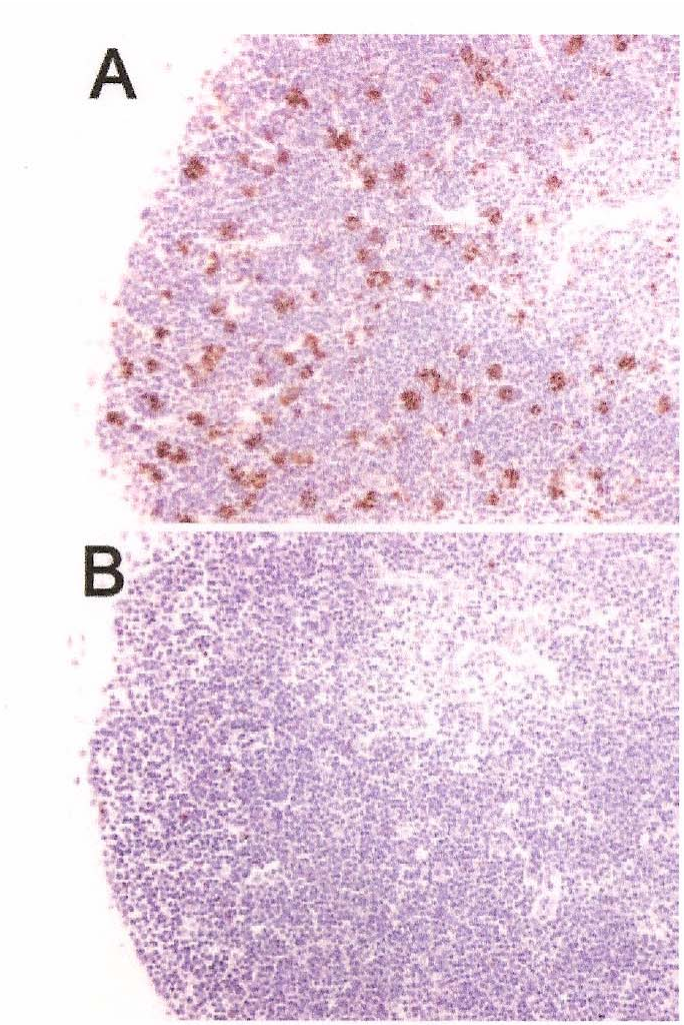


Figure 3. Decreased apoptosis caused by overexpression of Bcl-2 protein in a mouse model of plague. Wild-type mice (A) and mice that overexpressed Bcl-2 in lymphocytes (B) were injected intranasally with *Yersinia pestis*. Thymuses were obtained at 72 h postinfection and stained by using the terminal deoxynucleotidyl (TUNEL) method as a marker of apoptotic cell death. Note the decrease in apoptotic cells in the thymus of the Bcl-2 transgenic mouse (magnification ×400).

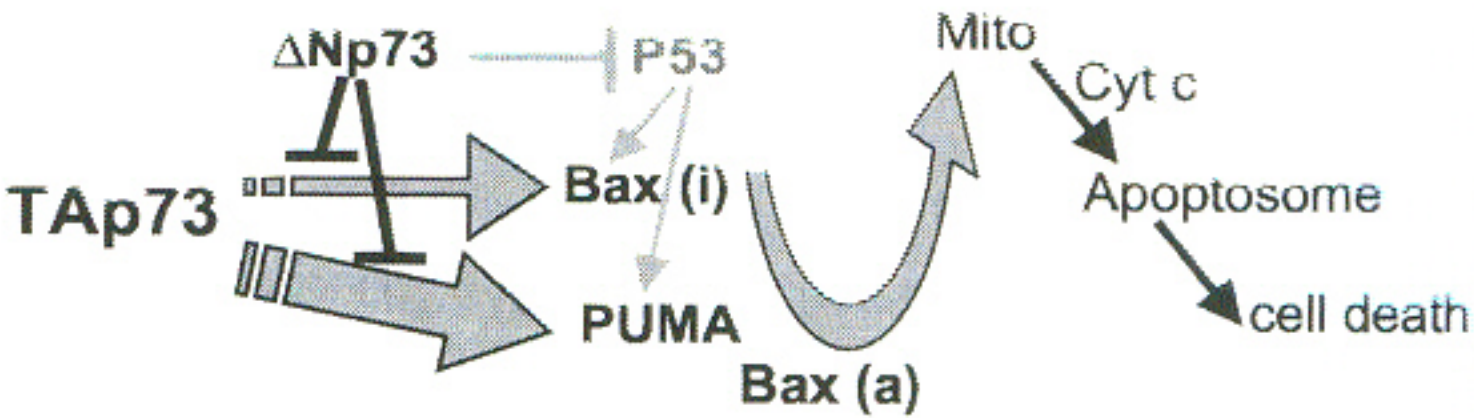


FIG. 8. **p73 induces apoptosis via PUMA-mediated Bax mitochondrial translocation.** A schematic representation of the p73 downstream mediators of cell death is shown. p73 transcriptionally regulates both Bax and PUMA. Although Bax induction is not sufficient to trigger apoptosis, PUMA causes mitochondrial relocalization of Bax, thus triggering mitochondrial cytochrome *c* release and, in turn, leading to apoptotic cell death. The ΔNp73 protein (and, similarly, other cancer-specific isoforms with deletion of the transactivating domain), regulated by a distinct promoter, inhibits TAp73 and p53 transcriptional properties, hence having anti-apoptotic effects.

JBC, 279 (9), 2004

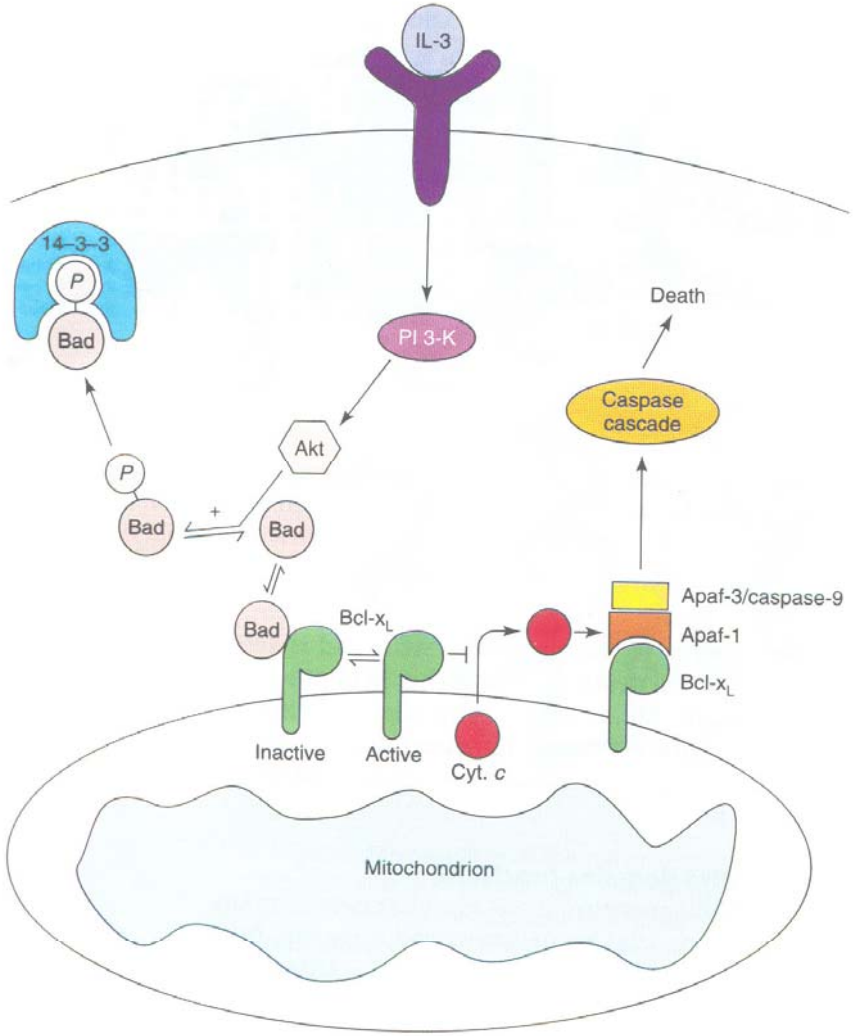


FIGURE 5

Model of a survival signalling pathway involving the BH3-containing protein Bad. Activation of the receptor for interleukin 3 (IL-3) mediates sequential activation of phosphoinositide 3-kinase (PI 3-K) and Akt, resulting in the phosphorylation (*P*) of Bad at Ser136. Bad can also be phosphorylated in a regulated manner at Ser112. The kinase(s) responsible for this phosphorylation have not been identified. Phosphorylated Bad is sequestered by the phosphoserine-binding protein 14–3–3. In the absence of IL-3 receptor occupation, Bad is hypophosphorylated or dephosphorylated and binds to Bcl-x_L, thus antagonizing its function. Inactive Bcl-x_L is unable to prevent the translocation of cytochrome *c* (Cyt. *c*) to the cytosol. Cyt. *c* release results in the activation of a caspase cascade through Apaf-1 and caspase-9 (Apaf-3).

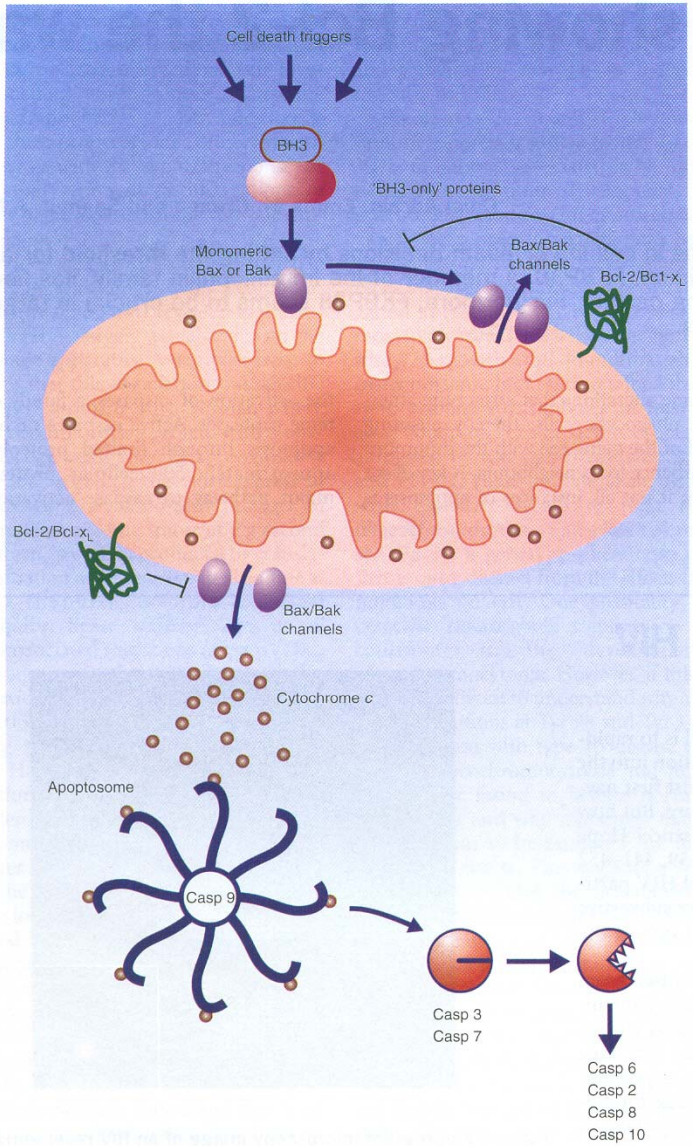


Figure 1 **The mitochondrial apoptosome route to apoptosis. Diverse cell death triggers converge on mitochondria to promote release of proteins from the mitochondrial intermembrane space, such as cytochrome *c*. In many instances, BH3-only members of the Bcl-2 family function as ligands for mitochondrial channels that facilitate the escape of mitochondrial proteins. In the cytosol, cytochrome *c* functions as a cofactor for assembly of the apoptosome, which drives the activation of caspase-9 and several downstream caspases. Bcl-2 and Bcl-x_L antagonize apoptosis by blocking the release of cytochrome *c* and other mitochondrial constituents.**

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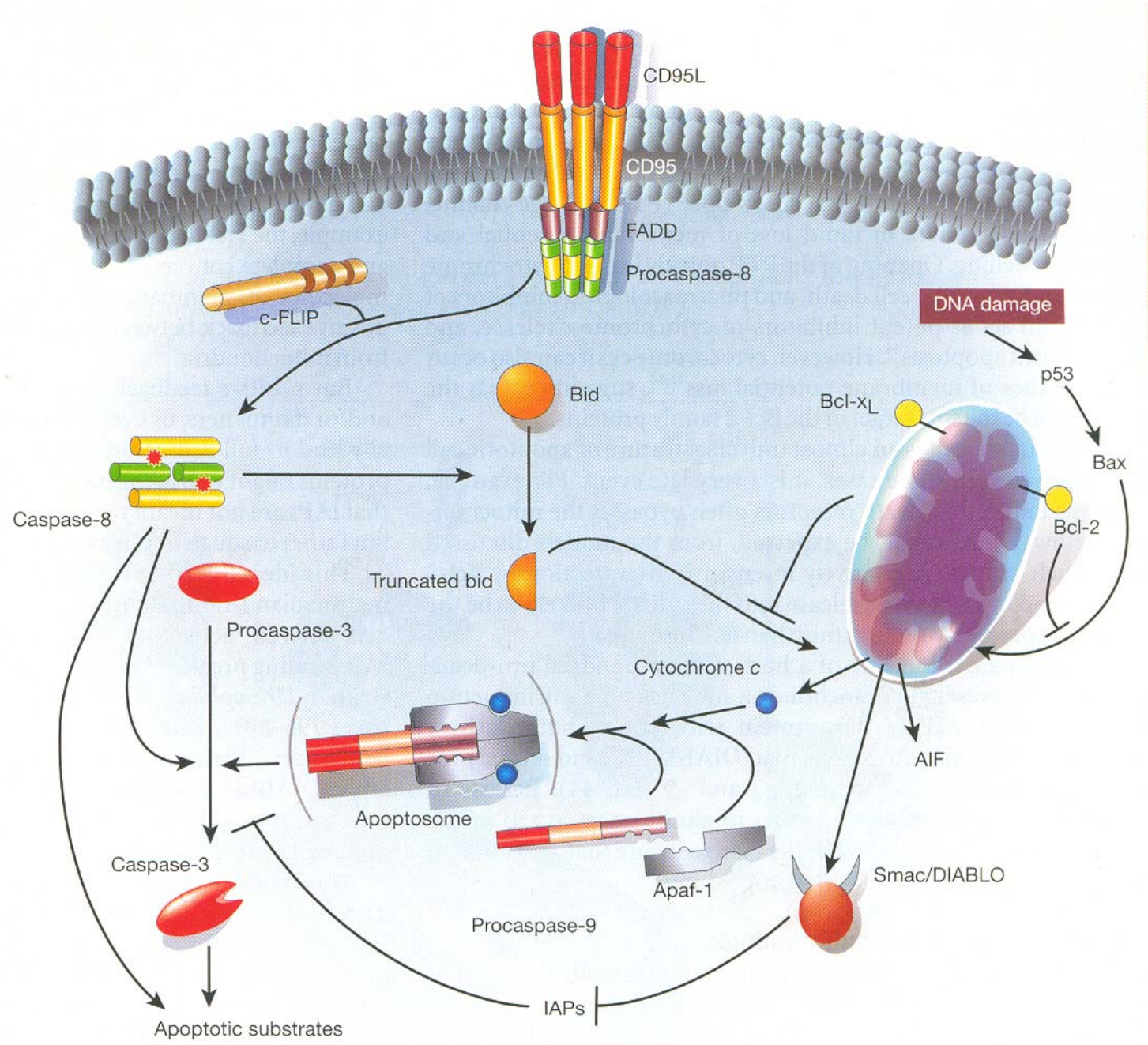

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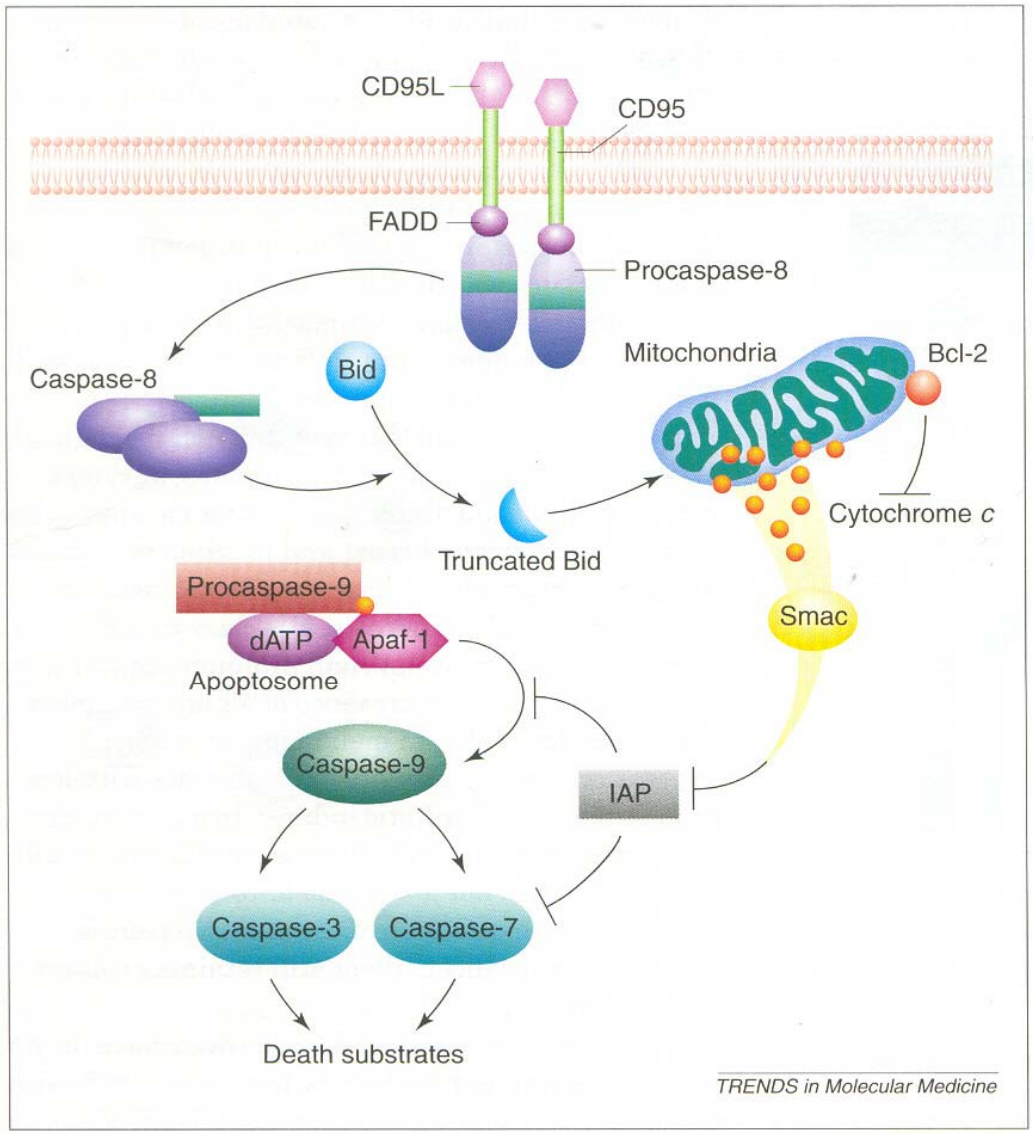


Fig. 1. General apoptotic pathways and modulation by inhibitor of apoptosis protein (IAP) family members. Cell-death pathways can be initiated by ligation of death receptors (e.g. CD95), resulting in activation of upstream caspase-8, or by release of mitochondrial cytochrome *c* in the cytoplasm. Cross-talk between the two pathways is provided by caspase-8-dependent cleavage of the Bcl-2 family member, Bid. The ability of IAP molecules to counteract the processing/function of upstream caspase-9 and effector caspase-3 and -7 is shown. Smac, a mitochondria-released protein, opposes IAP-dependent cytoprotection by releasing the bound caspase, favoring downstream completion of apoptosis.

Trends in Molecular Medicine, 7, 12, 2001

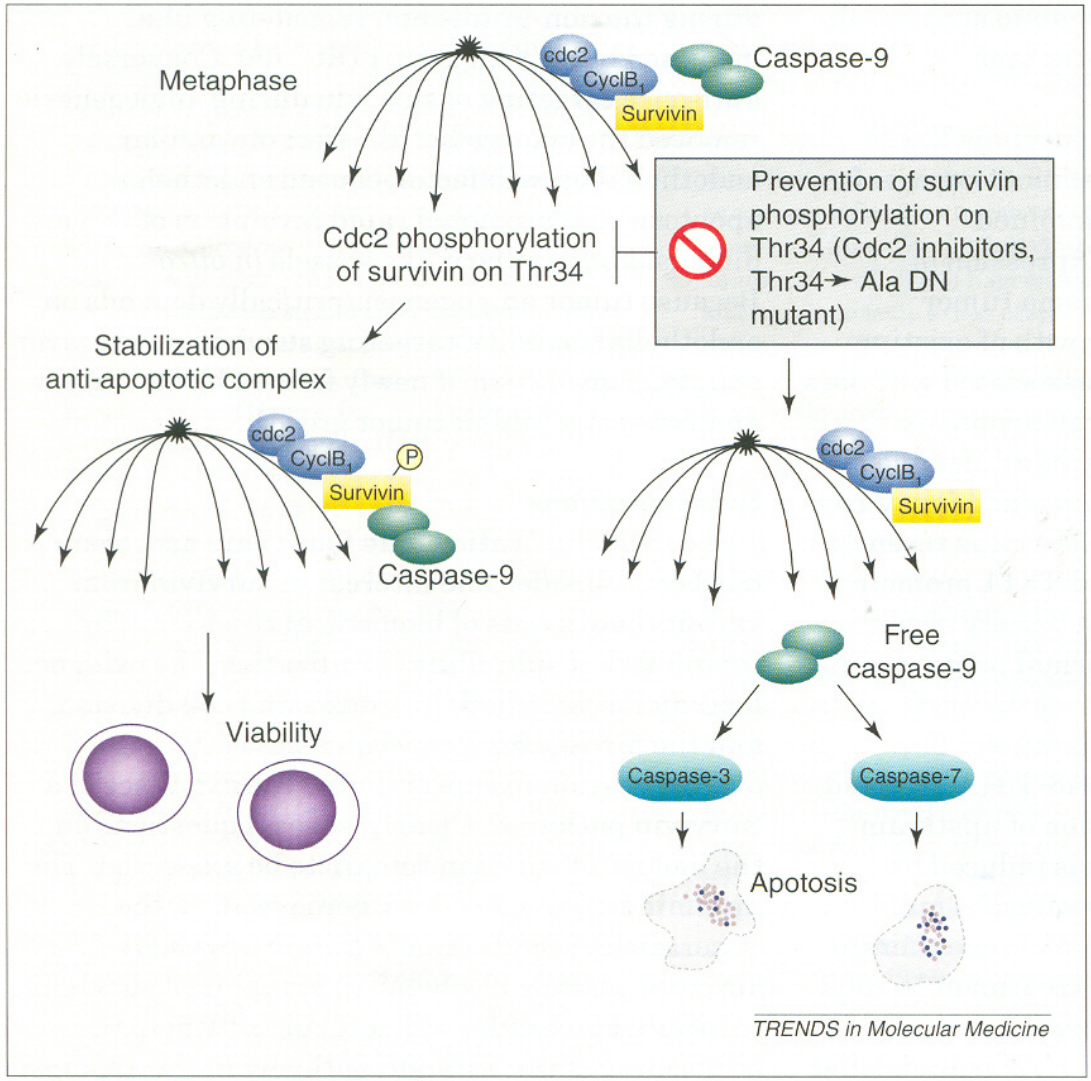


Fig. 4. Phosphorylation on Thr34 as a crucial requisite for survivin-dependent cytoprotection in cancer. A potential pathway of survivin-dependent cytoprotection in cancer cells requires mitotic phosphorylation on Thr34. At prometaphase, survivin complexes with the main mitotic kinase $p34^{cdc2}$-cyclin B1 on the mitotic apparatus, and is phosphorylated during mitosis by $p34^{cdc2}$-cyclin B1 on Thr34. Interference with survivin phosphorylation on Thr34 by expression of a phosphorylation-defective survivin Thr34→Ala dominant-negative (DN) mutant or by treatment with a cyclin-dependent kinase inhibitor results in the dissociation of a survivin–caspase-9 complex, mislocalization of caspase-9 from the mitotic apparatus and caspase-dependent apoptosis of cells traversing mitosis.

Trends in Molecular Medicine, 7, 12, 2001

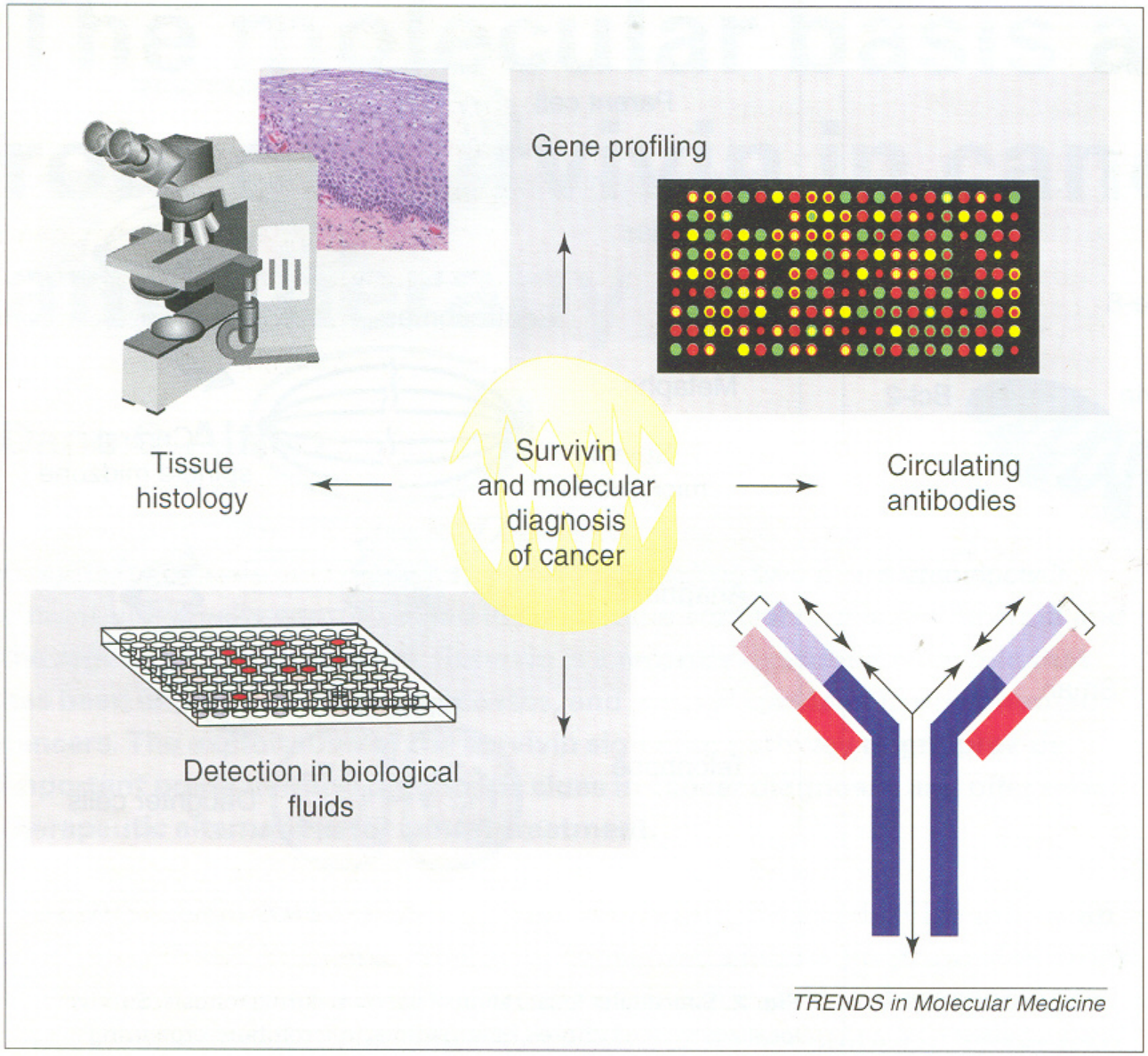
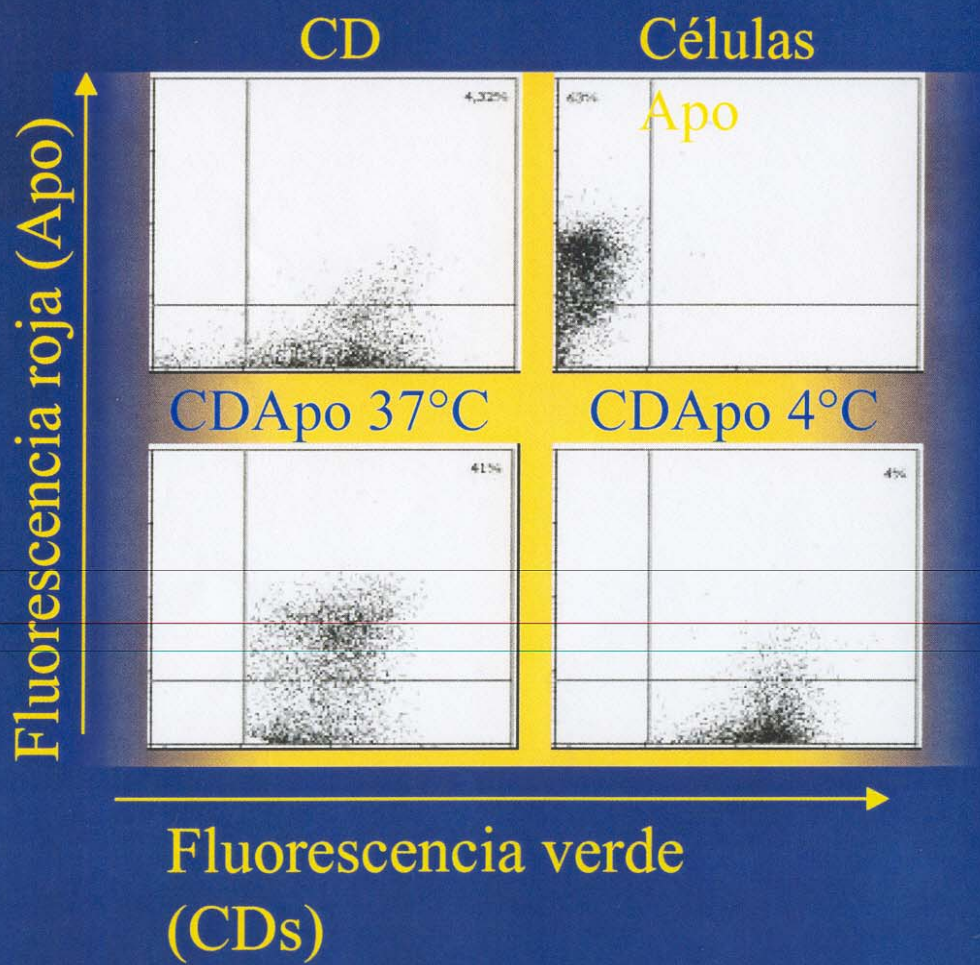


Fig. 3. Molecular diagnosis of cancer by survivin detection. Potential diagnostic applications of survivin in cancer patients includes immunohistochemical detection of survivin in tissue biopsies, microarray-based gene-profiling studies, direct detection in biological fluids (e.g. urine, serum, sputum), and determination of a cancer-specific immune response by assaying circulating antibodies to survivin.

Trends in Molecular Medicine, 7, 12, 2001

Cocultivo de células dendríticas y apoptóticas



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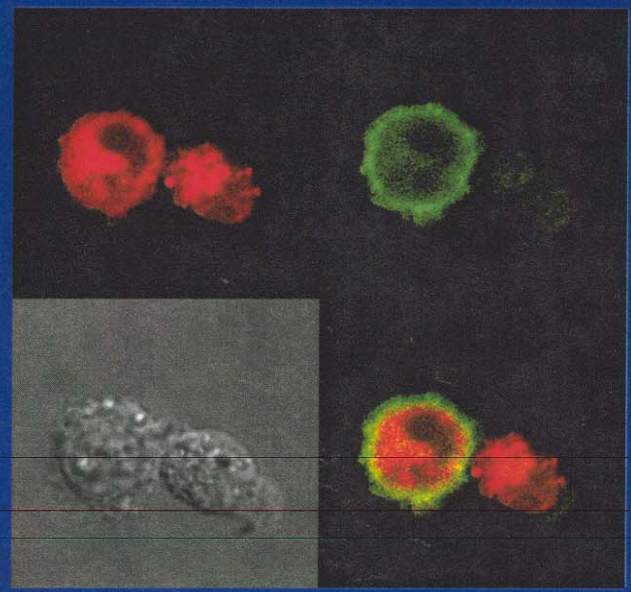

Células Apoptóticas

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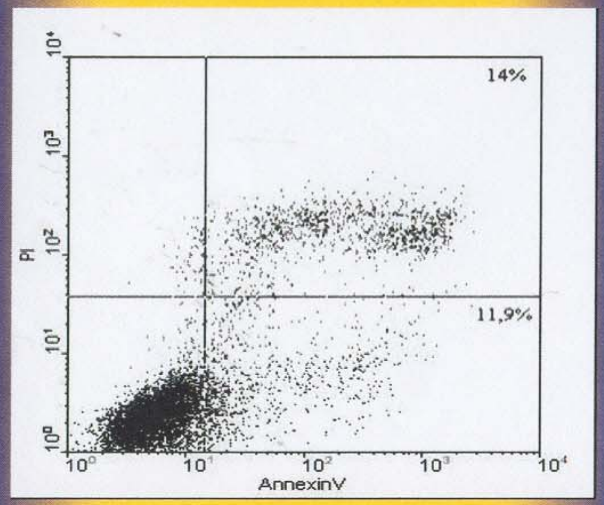

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