APOPTOSIS VÀ UNG THƯ

TS. BS Hoàng Anh Vũ
Đại học Y Dược TPHCM

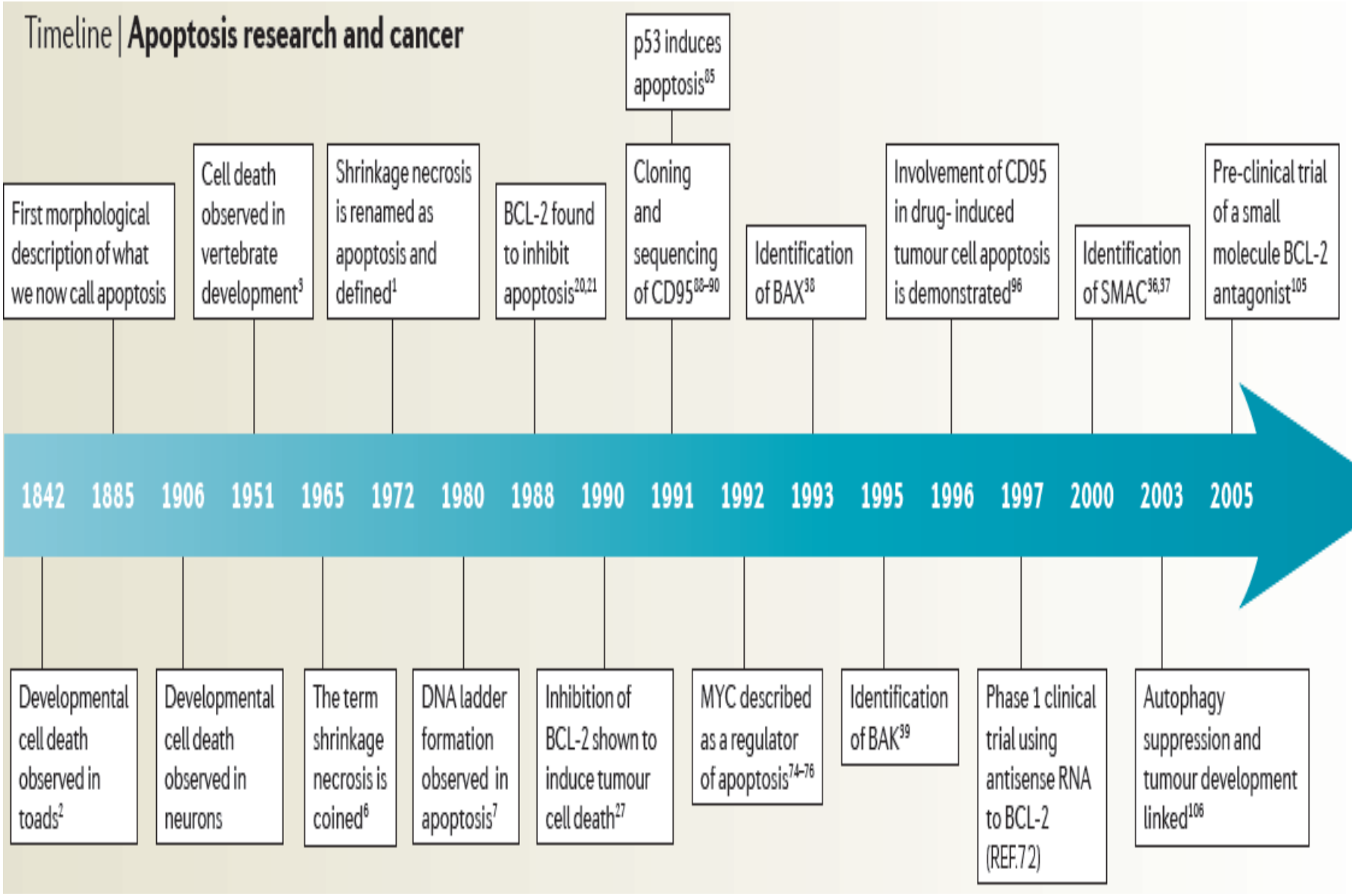
NỘI DUNG

1. **CÁC KIỂU CHẾT CỦA TẾ BÀO**
2. **CƠ CHẾ PHÂN TỬ CỦA HIỆN TƯỢNG APOPTOSIS**
3. **RỐI LOẠN APOPTOSIS TRONG UNG THƯ**
4. **CHIẾN LƯỢC ĐIỀU TRỊ DỰA TRÊN APOPTOSIS**

CÁC ĐẶC TÍNH CỦA TẾ BÀO UNG THƯ

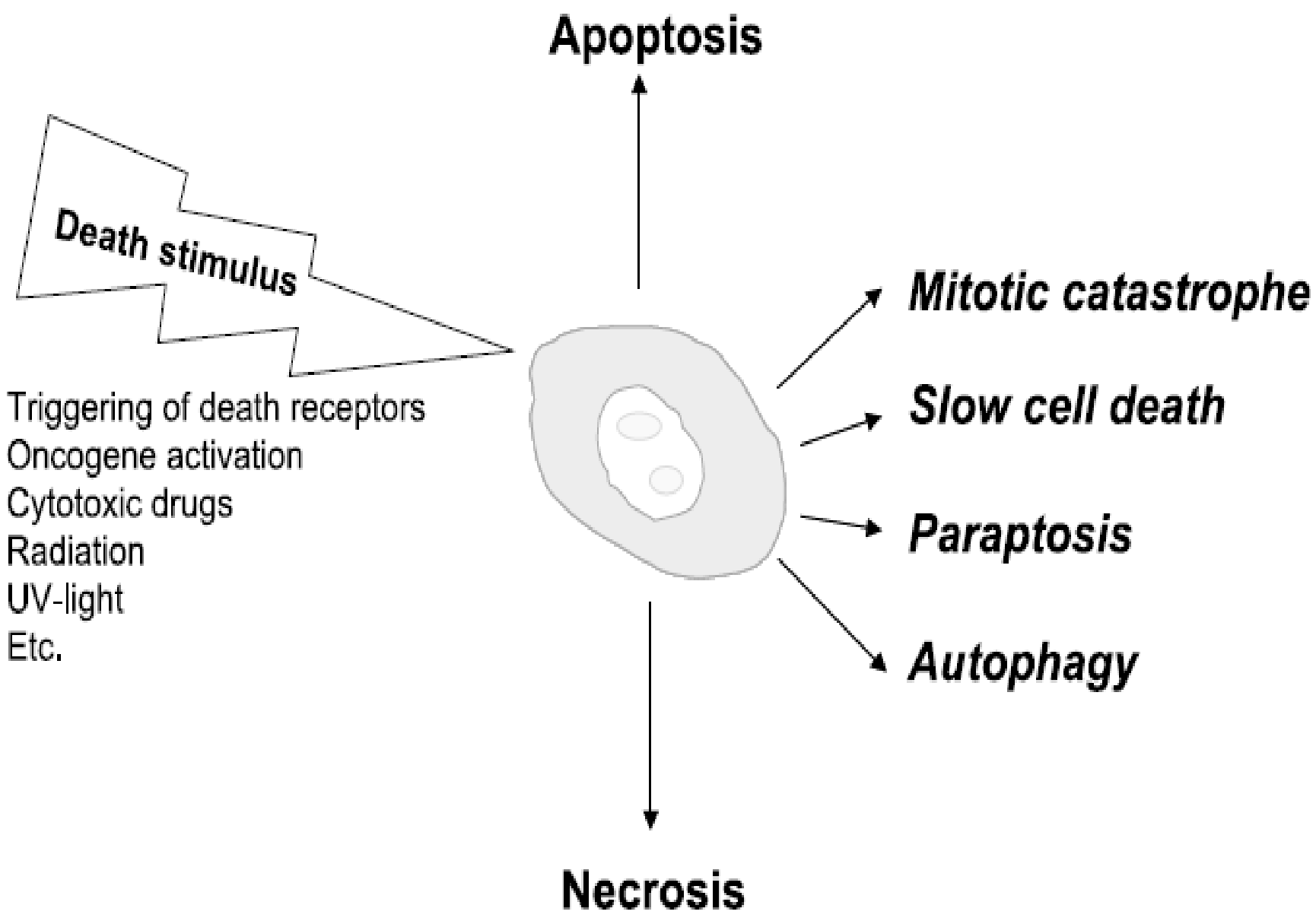
1. Không chịu sự tác động của tín hiệu nội bào và ngoại bào trong tăng sinh tế bào
2. Có khuynh hướng lẩn tránh chết tế bào theo lập trình
3. Không tuân thủ sự biệt hóa bình thường
4. Mất ổn định về mặt di truyền
5. Dễ “đi hoang” (escape from home tissues): xâm lấn
6. Sống sót và tăng sinh trong những vị trí mới: di căn

LỊCH SỬ NGHIÊN CỨU APOPTOSIS

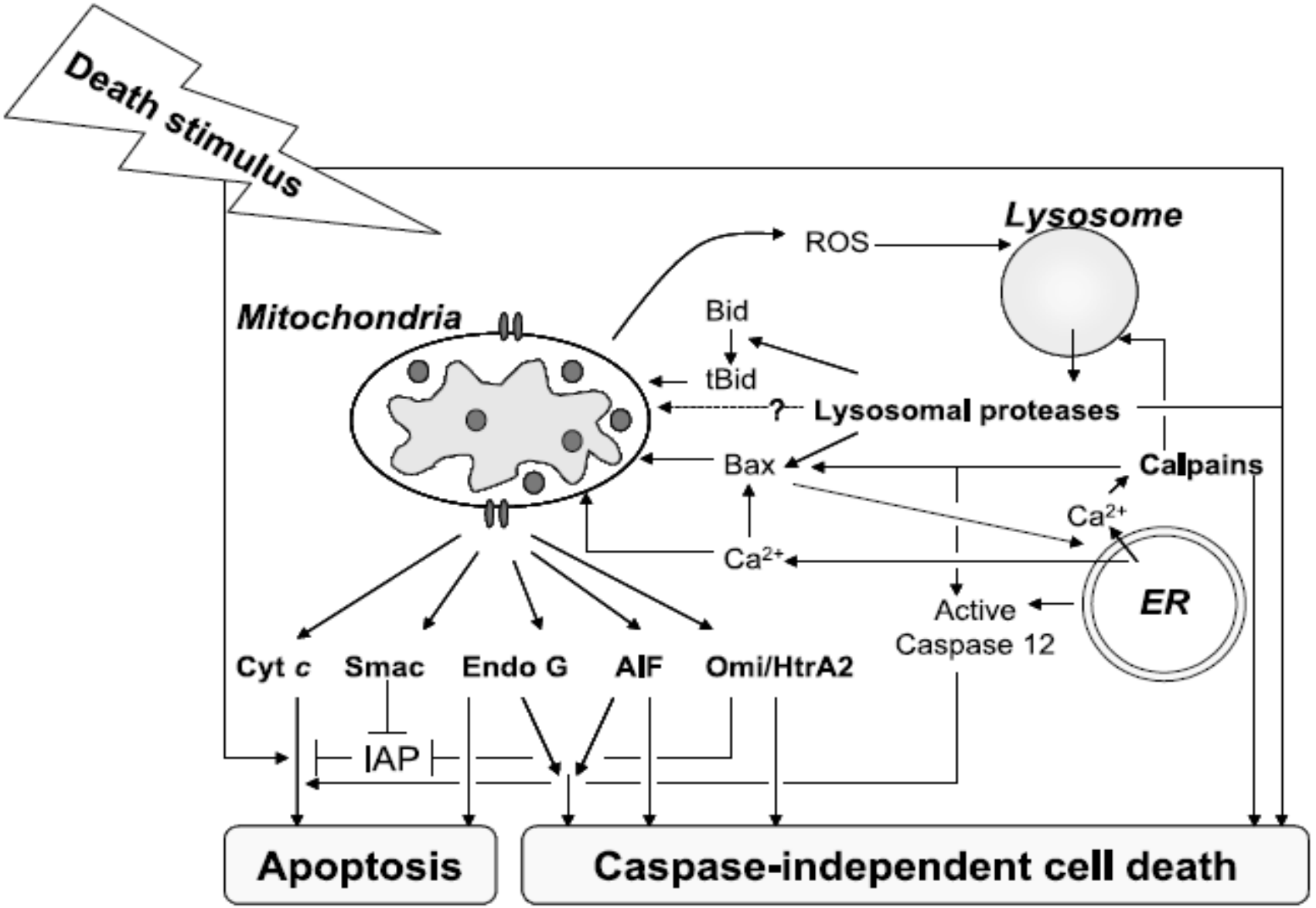


CÁC KIỂU CHẾT CỦA TẾ BÀO

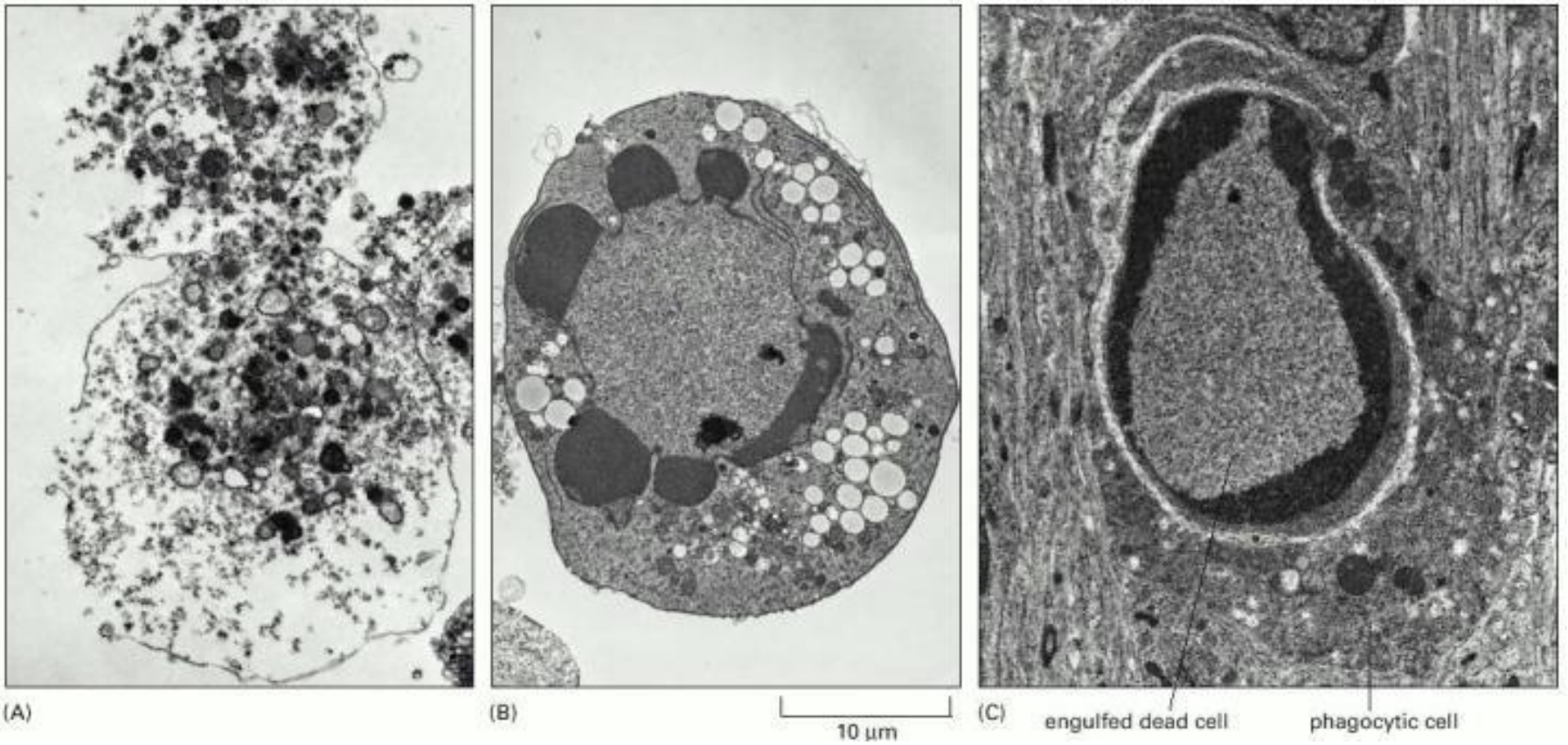
1. HOẠI TỬ (NECROSIS)
2. CHẾT THEO LẬP TRÌNH TYPE I (PROGRAMMED CELL DEATH: APOPTOSIS, ANOIKIS)
3. CHẾT THEO LẬP TRÌNH TYPE II (AUTOPHAGY: TỰ TIÊU)
4. MITOTIC CATASTROPHE


Apoptosis
Death stimulus
Triggering of death receptors
Oncogene activation
Cytotoxic drugs
Radiation
UV-light
Etc.
Mitotic catastrophe
Slow cell death
Paraptosis
Autophagy
Necrosis

CÁC BÀO QUAN GÂY CHẾT TẾ BÀO



NECROSIS VÀ APOPTOSIS



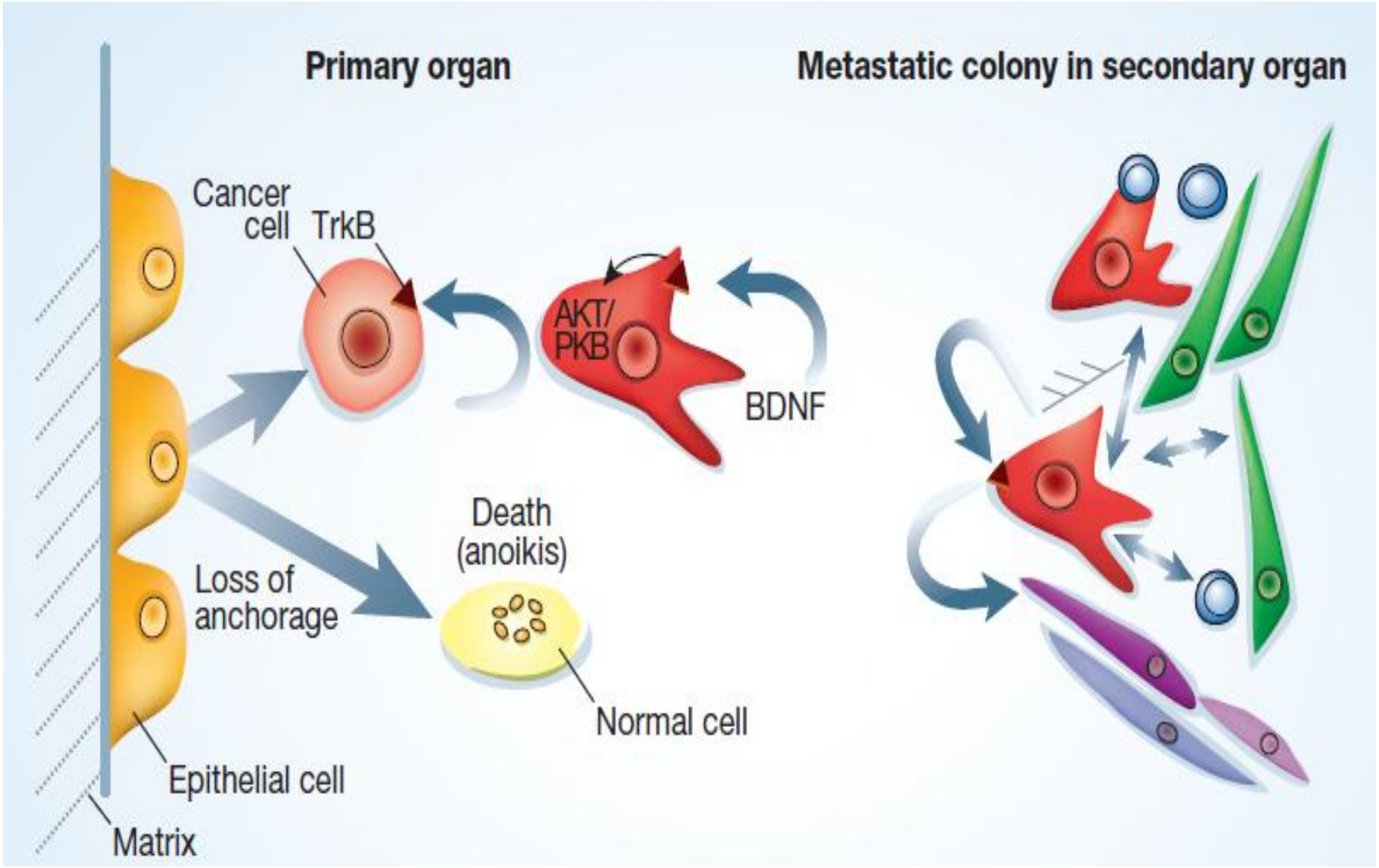
(A) Necrosis:

- Do tổn thương cấp tính
- Tế bào phồng và vỡ
- Phóng thích chất gây viêm

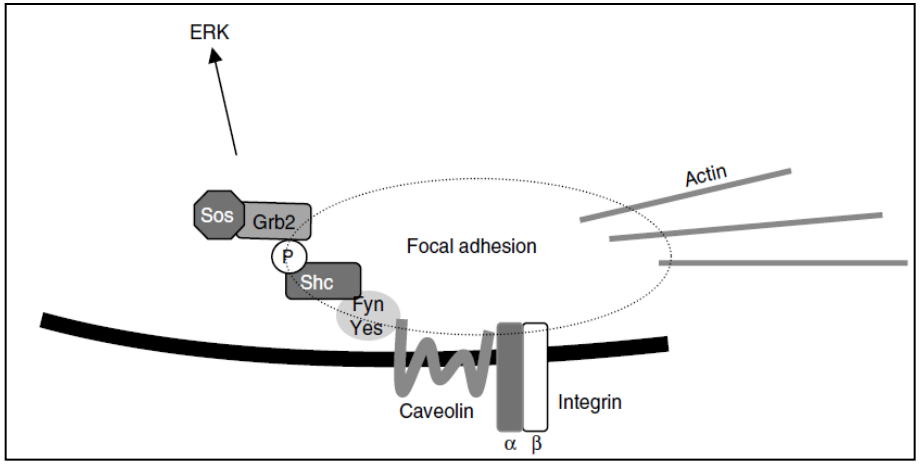
(B) Apoptosis: FALLING OFF

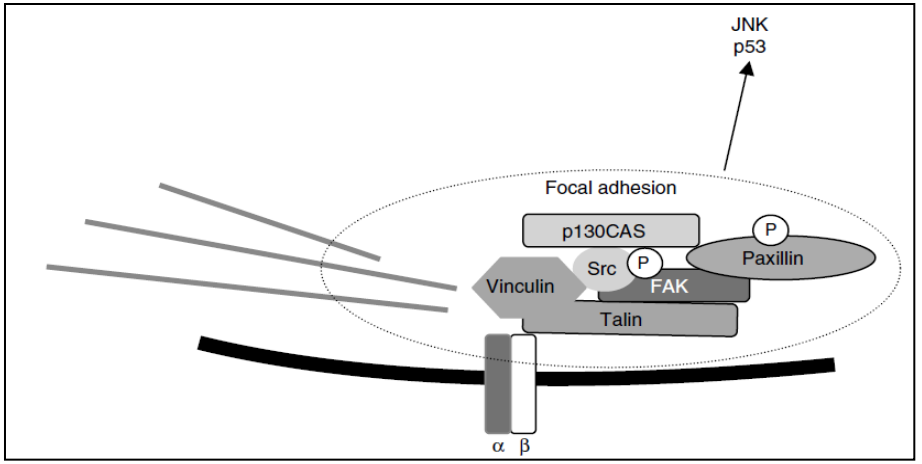
- Đã được lập trình
- Tế bào co nhỏ, khung tế bào sụp đổ, nhiễm sắc chất cô đặc, DNA nhân bị gãy vụn
- Không gây tổn hại xung quanh

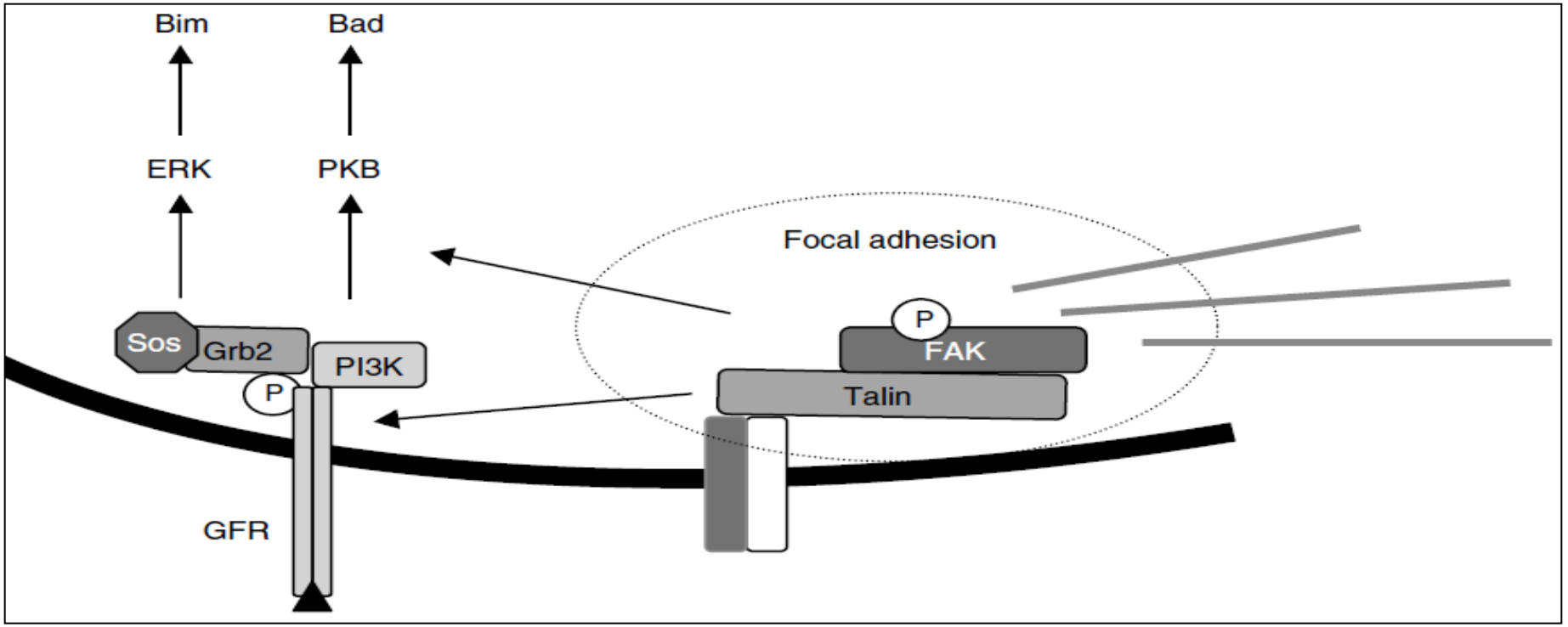
ANOIKIS
(HOMELESSNESS)



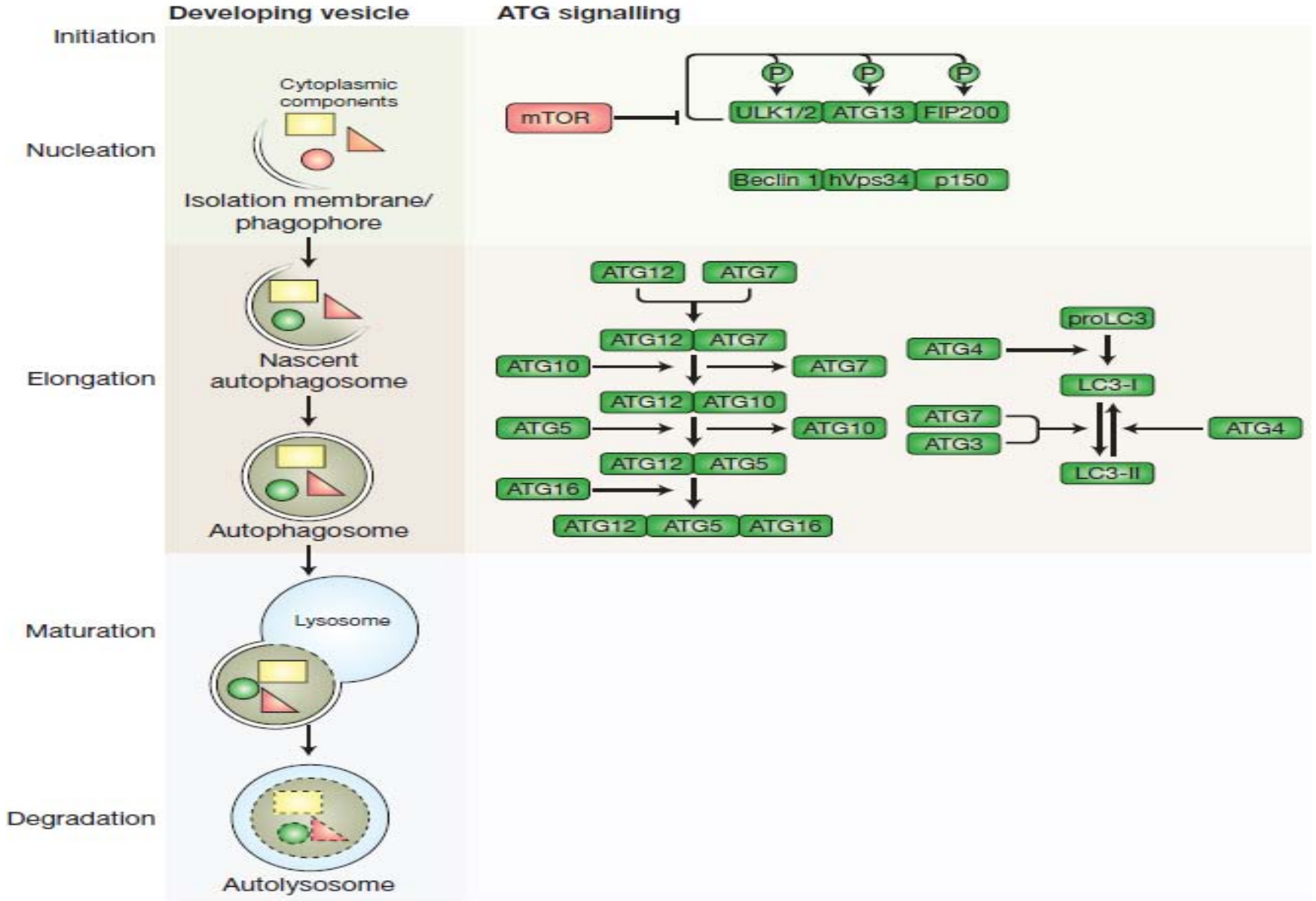
FOCAL ADHESION VÀ ANOIKIS





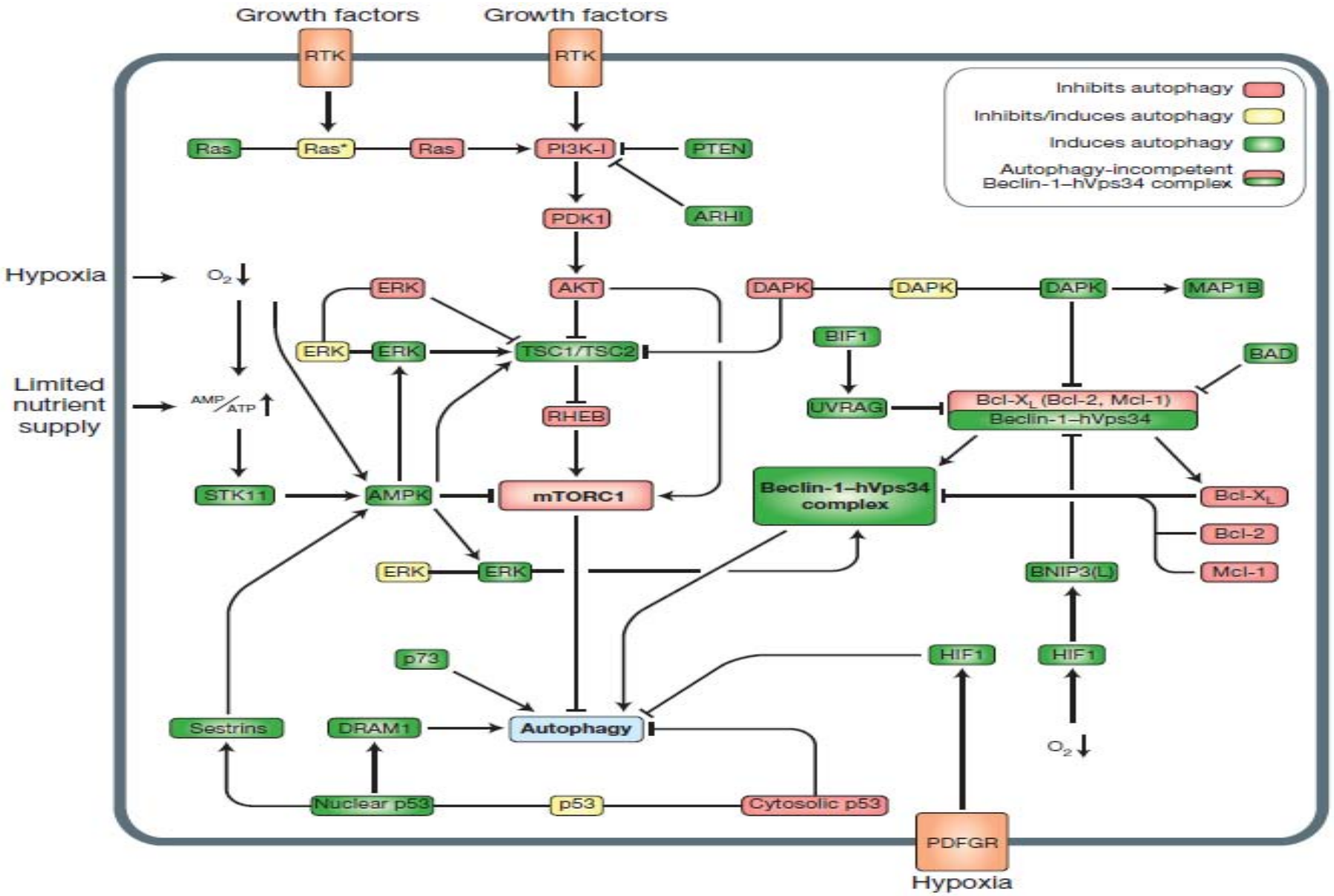


AUTOPHAGY

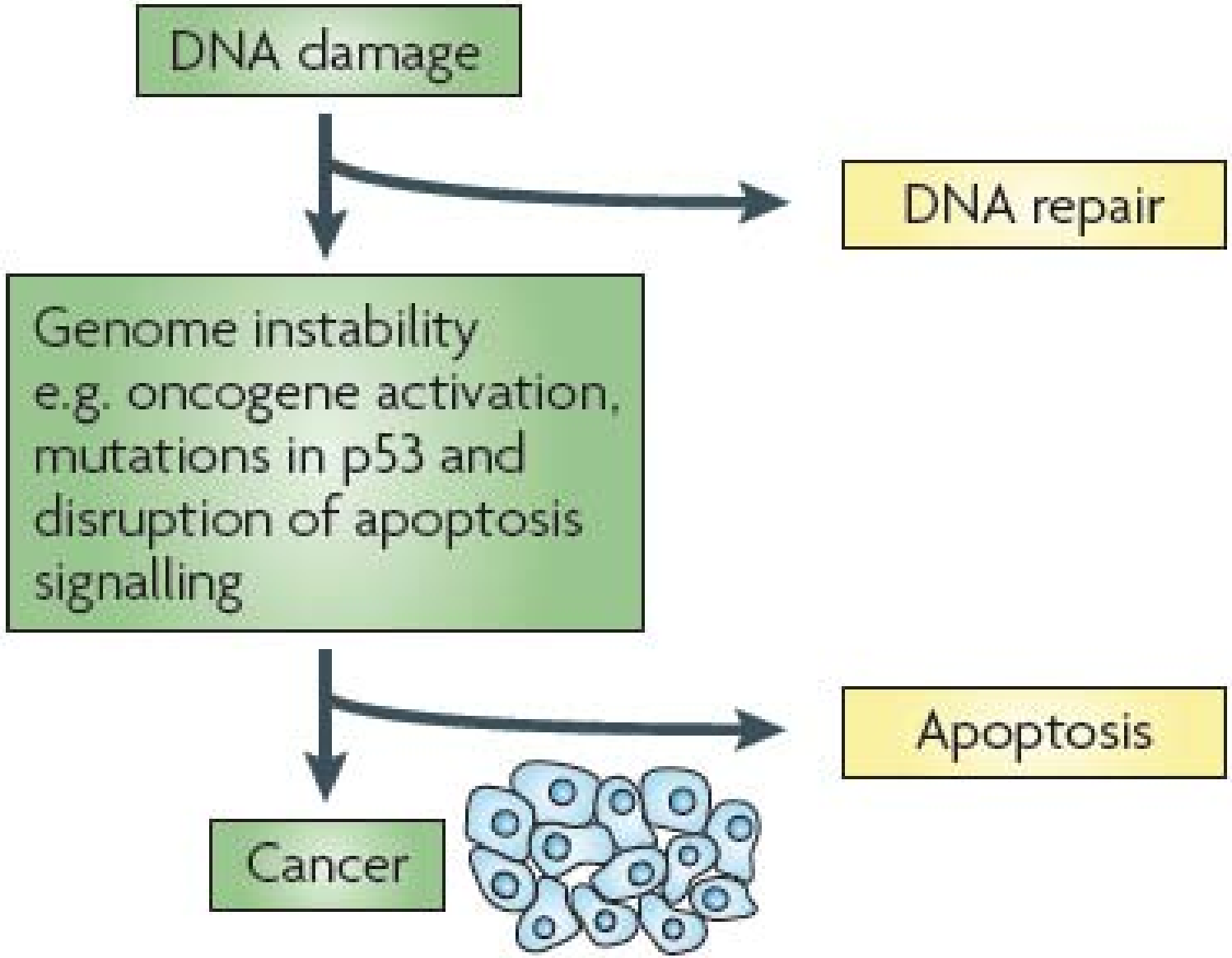


Mechanisms of autophagy

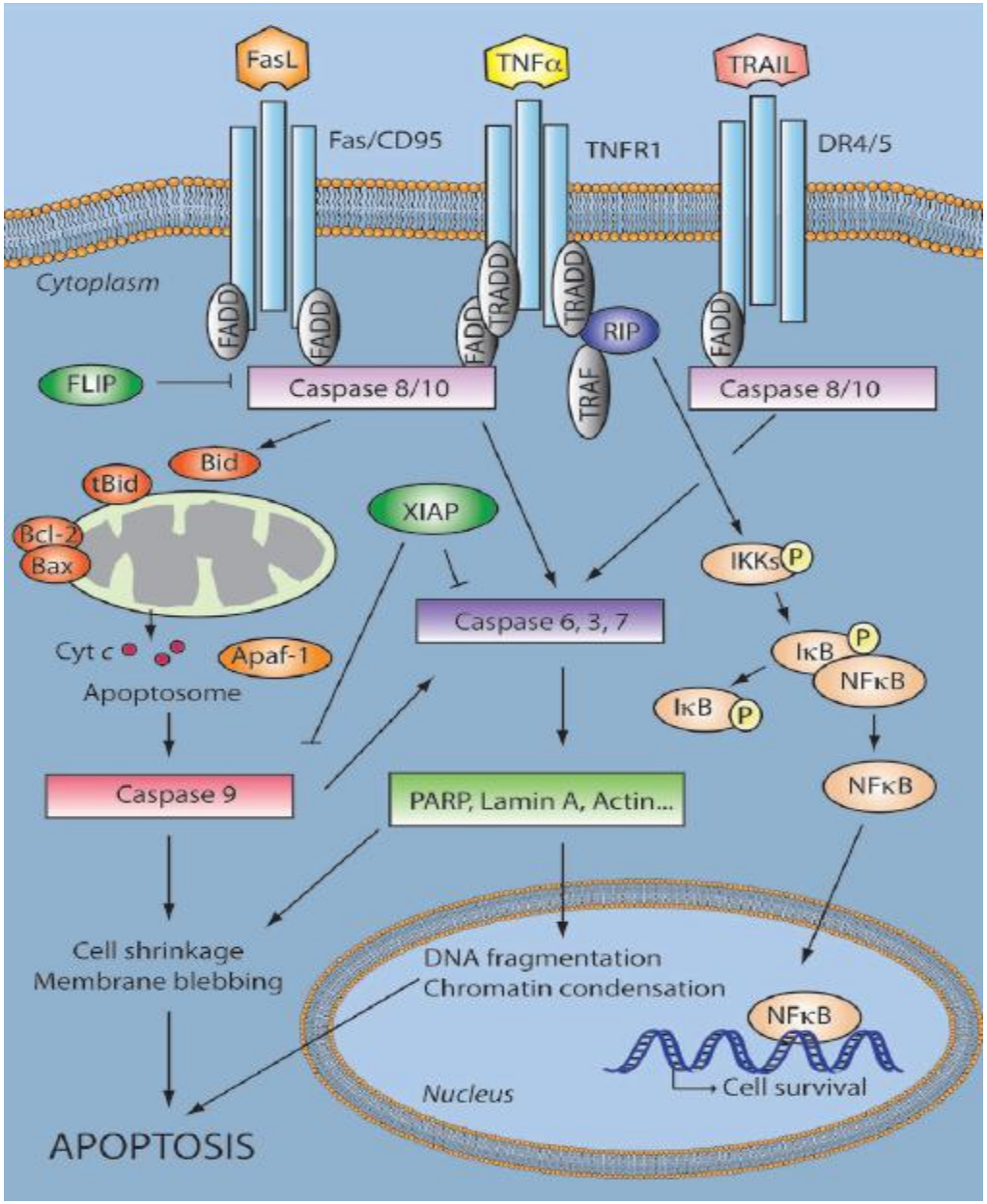
ĐIỀU HÒA AUTOPHAGY



Signalling networks of oncogenes and tumour suppressors that control autophagy


DNA damage
DNA repair
Genome instability
e.g. oncogene activation,
mutations in p53 and
disruption of apoptosis
signalling
Apoptosis
Cancer

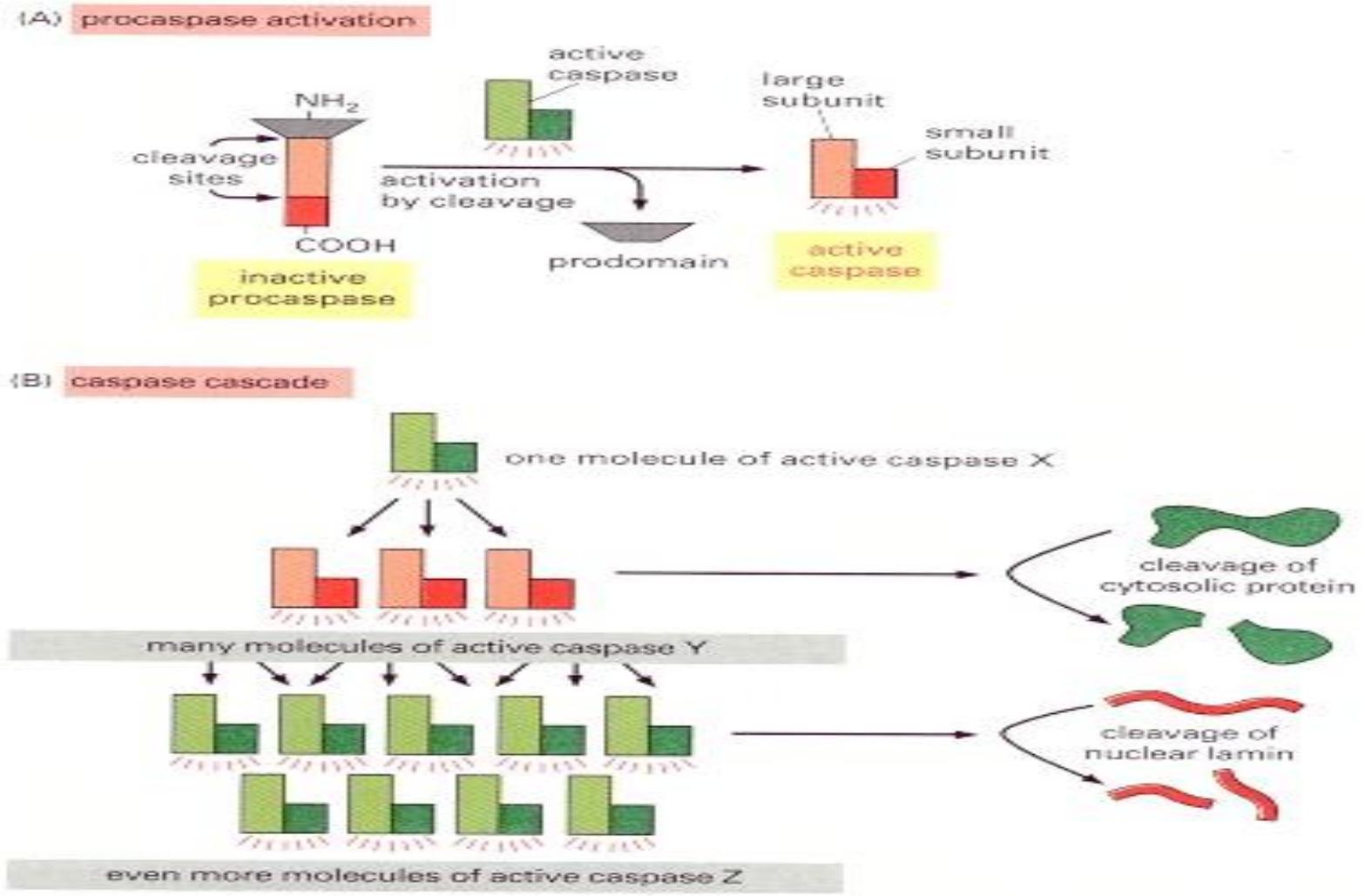
APOPTOSIS SIGNALLING NETWORK



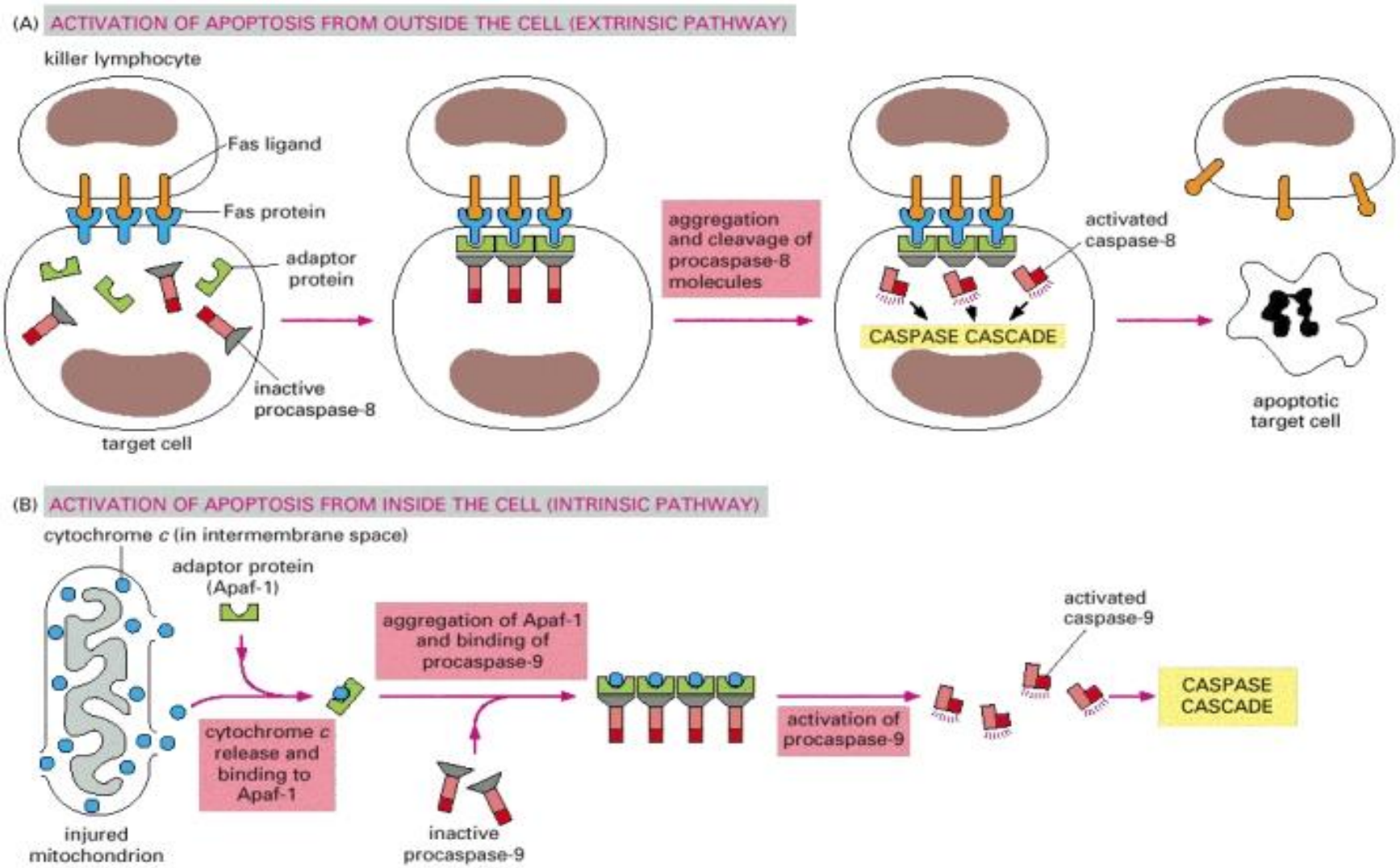
The extrinsic apoptosis pathway is activated upon ligand binding to death receptors (TNFR1,Fas/CD95, DR4/5). This results in activation of a caspase cascade and eventually cleavage of both cytoplasmic and nuclear substrates. TNFR1 may promote survival signalling through activation of NFκB. **The intrinsic pathway** involves release of apoptotic proteins from the mitochondria, formation of the apoptosome and subsequently caspase activation. Members of the BCL-2 protein family are involved in regulation of the intrinsic apoptotic pathway. The extrinsic and the intrinsic pathways converge in a caspase cascade that results in cellular shrinkage, DNA fragmentation and eventually apoptosis. Tumour necrosis factor receptor (TNFR), Tumour necrosis related apoptosis-inducing ligand (TRAIL), TNFR type 1-associated death domain protein (TRADD), Death receptor (DR), Fas-associated protein with death domain (FADD), TNFR associated factor (TRAF), Receptor interacting protein (RIP), FLICE-like inhibitory protein (FLIP), X-linked inhibitor of apoptosis protein (XIAP), Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), Inhibitor of κB (IκB), IκB kinases (IKKs), cytochrome *c (Cyt c), Apoptotic* protease activating factor 1 (Apaf-1).

HOẠT HÓA CASPASE

CASPASE: Protease có cysteine tại điểm hoạt động và ly giải protein đích tại vị trí aspartic acid



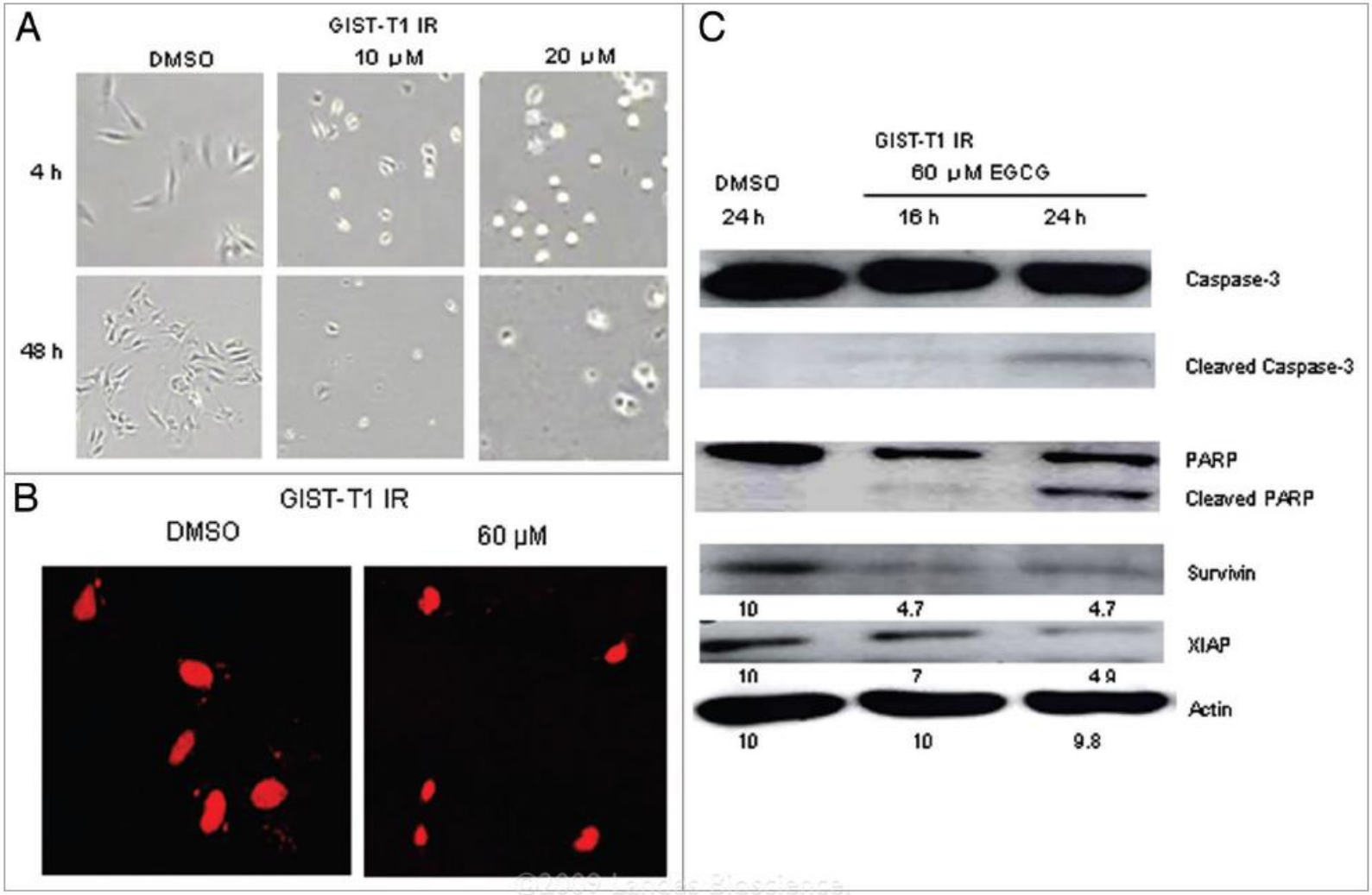
HOẠT HÓA CASPASE



Green tea (-)-epigalocatechin-3-gallate inhibits KIT activity and causes caspase-dependent cell death in gastrointestinal stromal tumor including imatinib-resistant cells

Hoang Thanh Chi,[1,2] Hoang Anh Vu,[1] Reo Iwasaki,[1,2] Le Ba Thao,[1,2] Yukihiko Hara,[3] Takahiro Taguchi,[4] Toshiki Watanabe[2] and Yuko Sato[1,*]

Cancer Biology & Therapy 8:20, 1-6; 15 October, 2009;



Apoptosis and cancer: mutations within caspase genes

Table 1 Summary of caspase-8 somatic mutation in gastric cancer

Tumour type	Total case numbers	Total cases with caspase-8 mutation	Cases with specific caspase-8 mutation	Mutation site	Mutation type	Nucleotide change (predicted amino acid change)
Gastric carcinoma[94]	162	15	1	Exon 1 (DED)	In-frame (deletion)	249_251 delGGA (E84del)
			1	Intron 2	Substitution	IVS2 + 1G >A (Unknown)
			1	Exon 1	Insertion	1_2insT (Unknown)
			1	Exon 1	Substitution	1A >G (Unknown)
			1	Exon 2 (DED)	Substitution (missense)	409A >C M137L
			2	Exon 3 (DED)	Deletion (frameshift)	492_493delTG (Frameshift after codon164 and stop at codon 178)
			1	Exon 3 (in between DED/p20)	Substitution (missense)	491G >A (C164Y)
			1	Exon 7 (p10)	Insertion (frameshift)	1223_1224 insT (Frameshift after codon 408 and stop at codon 438)
			1	Exon 6 (p20)	Deletion (frameshift)	698delG (Frameshift after codon 233 and stop at codon 237)
			2	Intron 6	Insertion	IVS6 + 47 insT (Unknown)
			1	Exon 7 (p20)	Deletion (frameshift)	969_972 delCTAT (Frameshift after codon 323 and stop at codon 335)
			1	Exon 8	Substitution (missense)	1427T >C (F476S)
			1	3′-Untranslated region	Insertion	*43 insT (Unknown)

(Ghavami S, *J Med Genet* 2009)

Apoptosis and cancer: mutations within caspase genes

Table 3 Summary of caspase-3 somatic mutation in different cancer

Tumour type	Total case numbers	Cases with caspase-3 mutation	Mutation site	Mutation type	Nucleotide change (predicted amino acid change)
Adenocarcinoma-stomach[133]	165	2	Exon 6 (p12 protease subunit)	Silent	667C→T (no change)
			Intron 4		IVS4 −64del A (no change)
Squamous cell carcinoma-lung and lung adenocarcinoma[133]	181	4	Exon 6 (p12 protease subunit)	Silent	667C→T (no change)
			Exon 6 (p12 protease subunit)	Missense	674A→T (Q225L)
			Exon 3 (p17 protease subunit)	Missense	278G→T (R93L)
			Exon 5 (p12 protease subunit)	Missense	553C→A (H185 N)
Adenocarcinoma- ascending colon	95	4	3′-untranslated region		*26del A (no change)
Adenocarcinoma- rectum			Exon 4 (p17 protease subunit)	Missense	469C→A (L157I)
Adenocarcinoma- descending colon			Exon 4 (p17 protease subunit)	Silent	579C→A (F193L)
Adenocarcinoma- descending colon[133]			Exon 6 (p12 protease subunit)	Silent	654G→A (no change)
Hepatocellular carcinoma[133]	80	1	5′-untranslated region		-7C→T (no change)
Multiple myeloma[133]	28	1	Intron 5		IVS5 +8C→T (no change)

Apoptosis and cancer: mutations within caspase genes

Table 5 Caspase-7 somatic mutations in different cancers

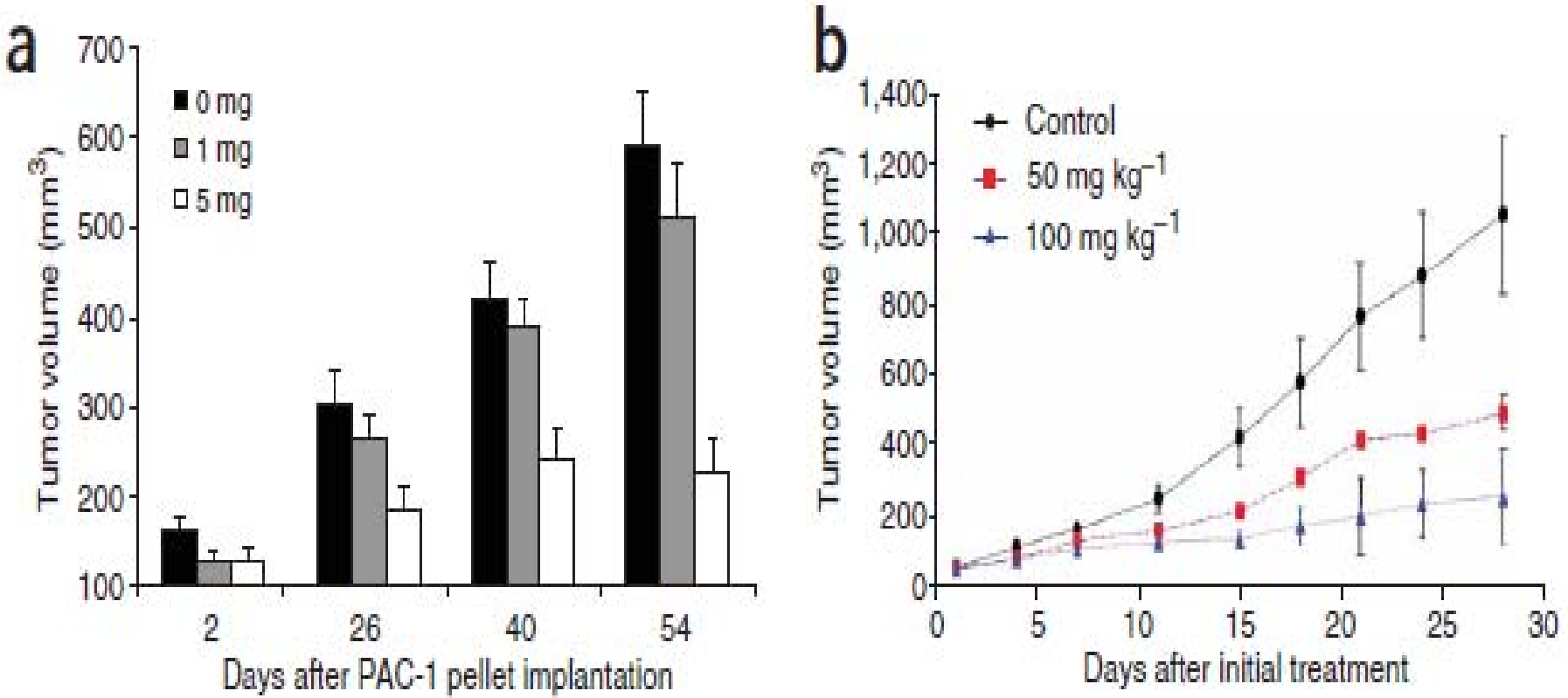
Tumour type	Total case numbers	Cases with caspase-7 mutations	Mutation site	Nucleotide change (predicted amino acid change)
Colon adenocarcinoma[139]	90	2	Exon 2	127 C to T (Arg 43 stop)
			Exon 3	384 A to G (no change)
Oesophageal squamous cell carcinoma[139]	50	1	Intron 1	IVS 1 C -3 to T (splice defect)
Laryngeal squamous cell carcinoma[139]	33	1	Exon 2	209 G to A (Cys 70 Tyr)

Apoptosis and cancer: mutations within caspase genes

Table 6 Caspase-1, -4, and -5 somatic mutations in different cancers

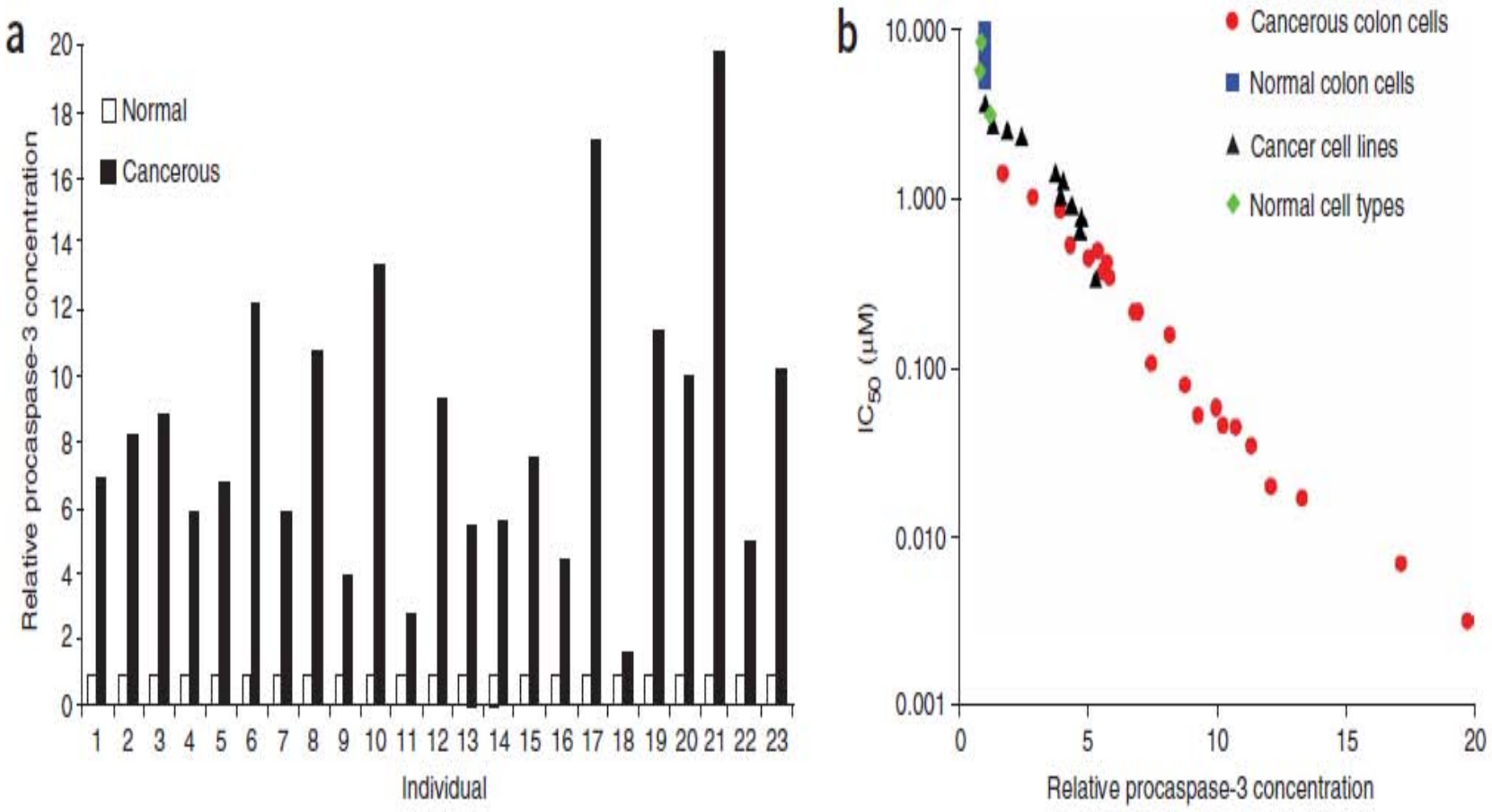
Caspase	Tumour type	Total case numbers	Cases with mutation	Mutation site	Nucleotide change (predicted amino acid change)
Caspase-1[142]	Gastric carcinoma	54	2	Exon 7 (p10)	1034 T>A (M345K)
				Intron 2	IVS2-3C>A (unknown)
Caspase-4[142]	Colon carcinoma	103	2	Intron 6	IVS6+9C>A (unknown)
				Exon 3 (p20)	346 G>T (R116I)
Caspase-5[142]	NSCLC (adenocarcinoma)	60	1	Exon 4 (p20)	629TNA (L210Q)
Caspase-5[142]	Colon carcinoma	103	4	Exon 2 (CARD domain)	153_154delAA (frameshift after codon 51 and stop at codon 68)
				Exon 2 (CARD domain)	154dupA (frameshift after codon 51 and stop at codon 68)
				5′-UTR	-21_-22AA (unknown)
				Intron 6	IVS6+6T>A (unknown)
Caspase-5[142]	Gastric carcinoma	54	9	5′-UTR (4 cases)	-21_-22AA (unknown)
				Exon 2 (CARD domain) (3 cases)	154delA (frameshift after codon 51 and stop at codon 77)
				Exon 2 (CARD domain)	153_154delAA (frameshift after codon 51 and stop at codon 68)
Caspase-5[142]	Breast carcinoma	60	1	Exon 1	105T>C (N35N)

Small-molecule activation of procaspase-3 to caspase-3 as a personalized anticancer strategy



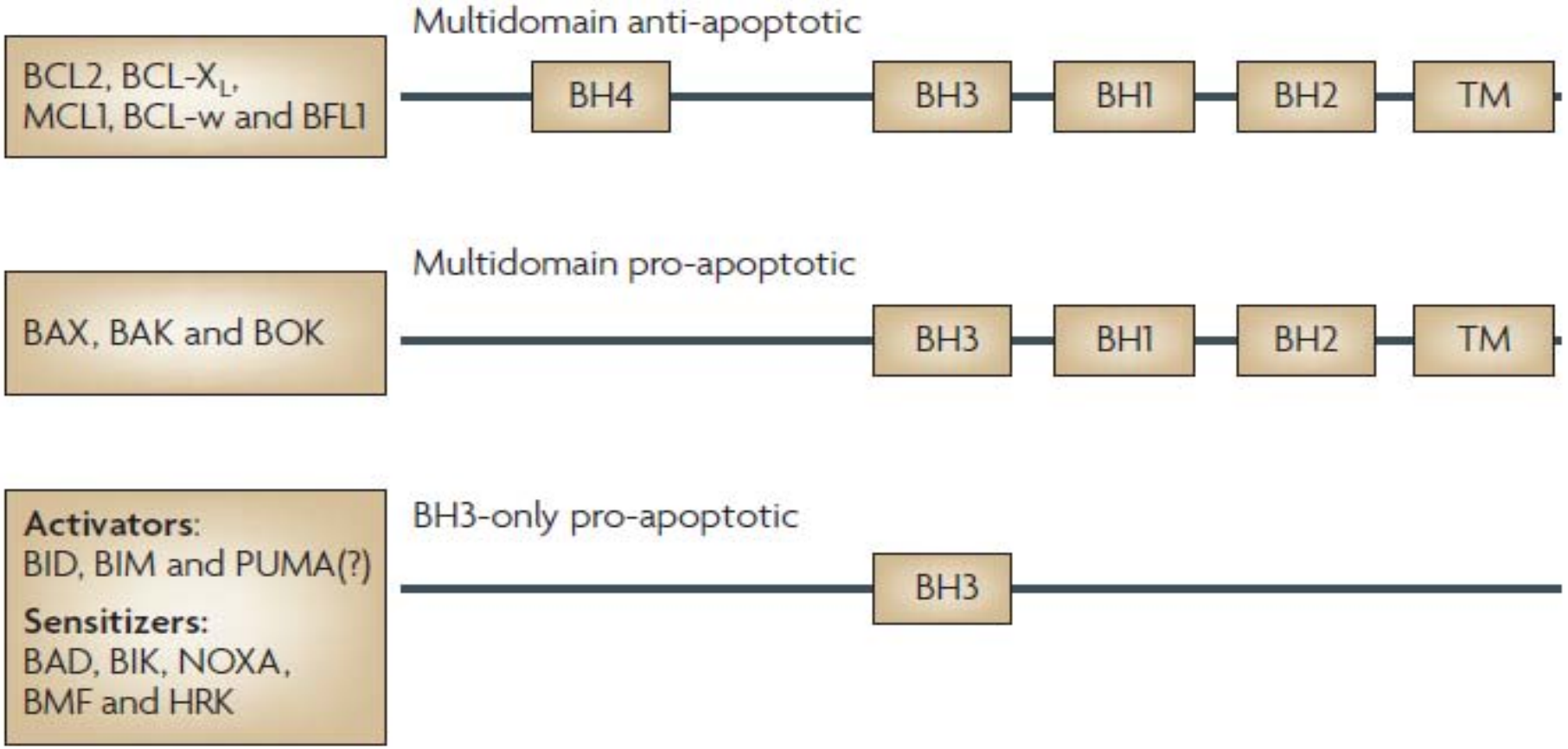
(Putt KS, *Nat Chem Biol* 2006)

Small-molecule activation of procaspase-3 to caspase-3 as a personalized anticancer strategy

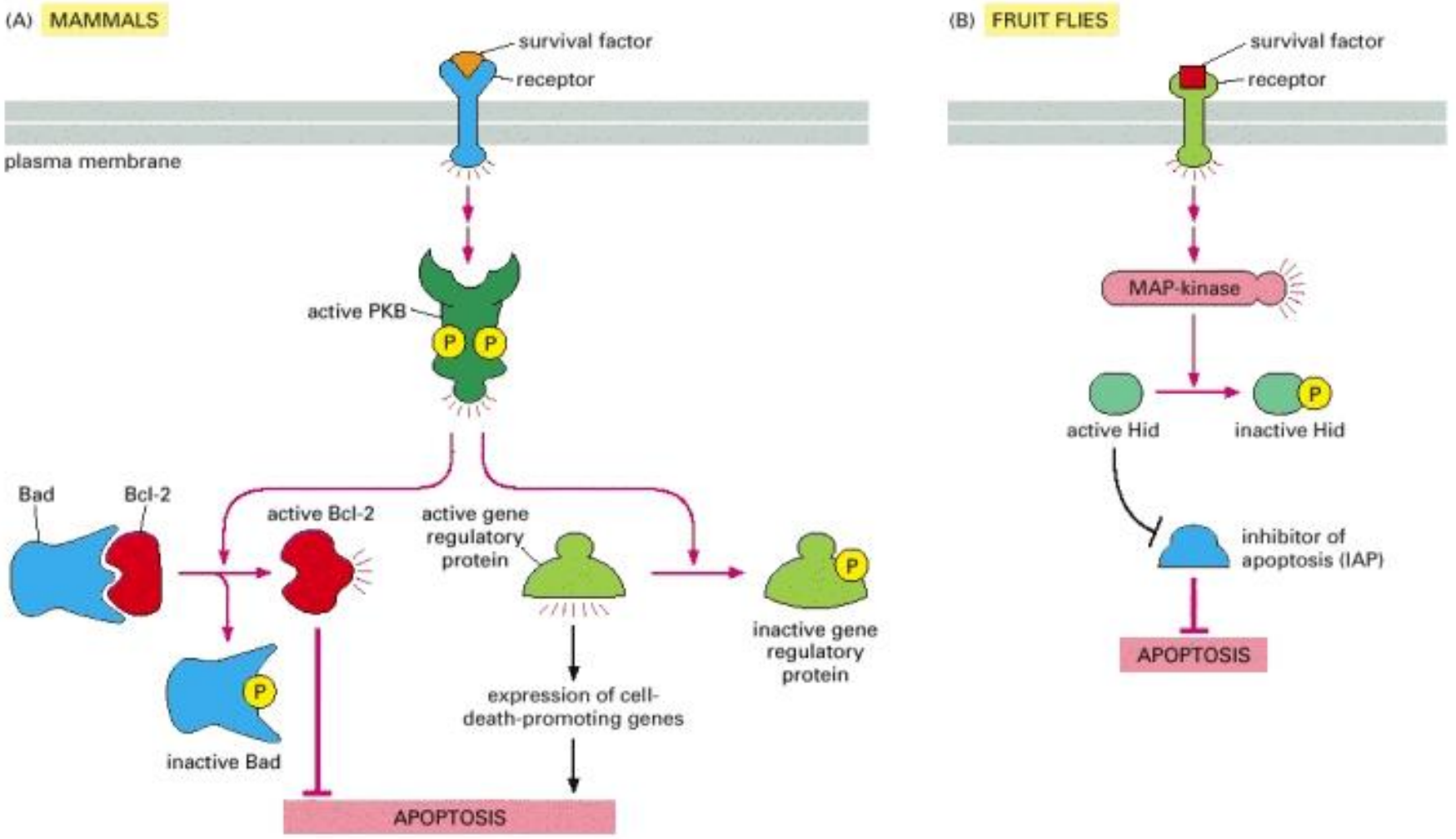


(Putt KS, *Nat Chem Biol* 2006)

BCL-2 FAMILY


Multidomain anti-apoptotic
BCL2, BCL-X_L, MCL1, BCL-w and BFL1
BH4
BH3
BH1
BH2
TM
Multidomain pro-apoptotic
BAX, BAK and BOK
BH3
BH1
BH2
TM
BH3-only pro-apoptotic
Activators:
BID, BIM and PUMA(?)
Sensitizers:
BAD, BIK, NOXA, BMF and HRK
BH3

SURVIVAL FACTORS SUPPRESS APOPTOSIS



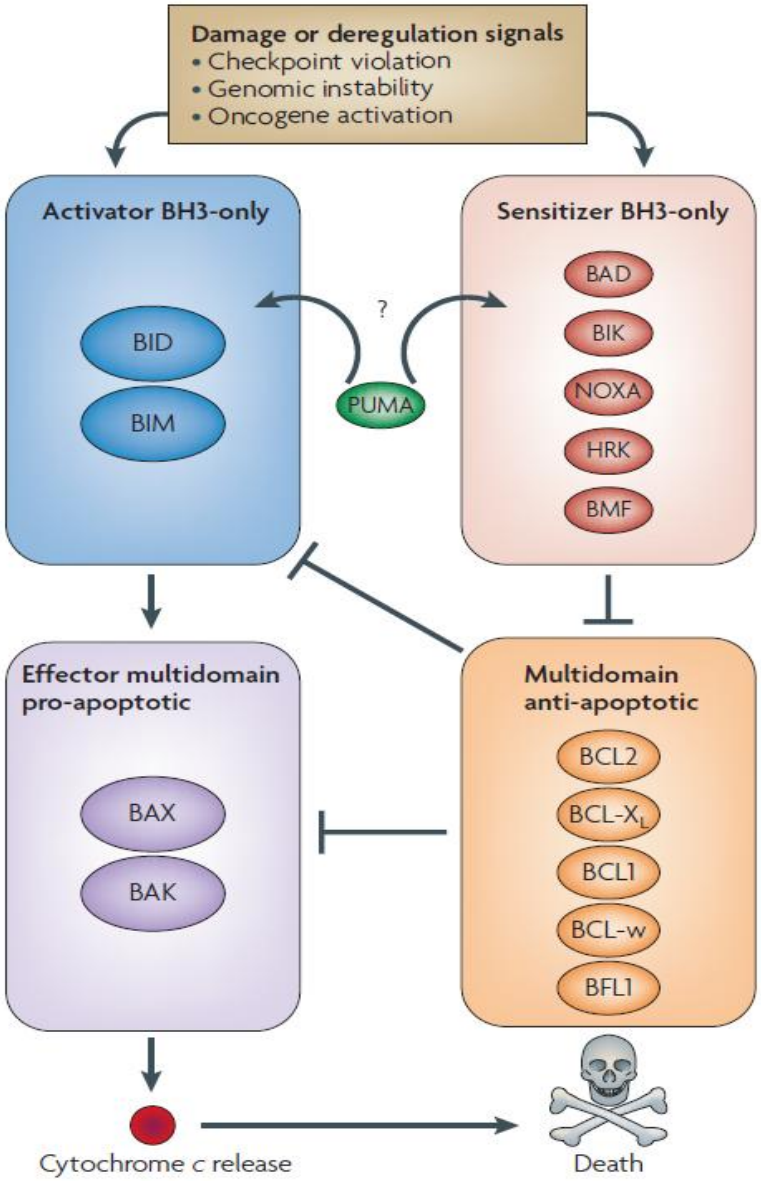


Figure 3 | **A model of BCL2 family control over mitochondrial apoptosis.** In response to cellular damage or deregulation, activator BH3-only proteins such as BH3-interacting domain death agonist (BID) or BIM are activated by transcription or post-translational modification. Activator BH3-only proteins activate effectors such as BCL2-associated X protein (BAX) and BCL2-antagonist/killer (BAK), inducing homo-oligomerization, resulting in mitochondrial permeabilization and commitment to death. Anti-apoptotic proteins sequester activators to prevent them contacting effectors, and also might sequester activated monomeric BAX or BAK. Sensitizers act as selective antagonists of anti-apoptotic proteins. Whether PUMA is a member of the sensitizer or activator class of BH3 proteins remains to be shown clearly, so it is placed in between the two classes in this figure. BAD, BCL2 antagonist of cell death; BID, BH3-interacting domain death agonist; BIK, BCL2-interacting killer; BMF, Bcl2-modifying factor; BOK, BCL2-related ovarian killer. Modified, with permission, from REF. 72

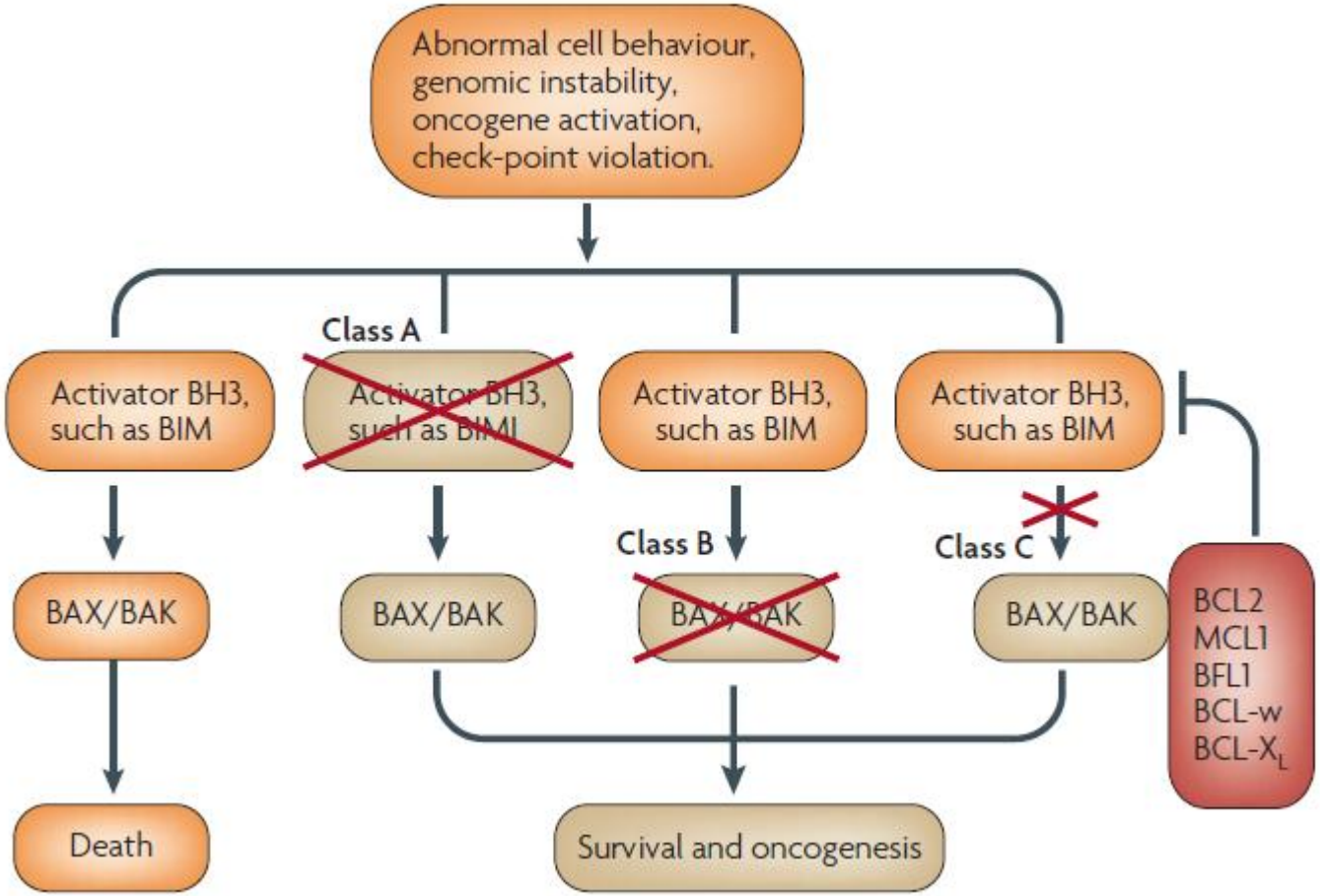


Figure 4 | **Three classes of apoptotic blocks used to maintain cancer survival.** Apoptosis is a tumour-suppressive mechanism that cancer cells must overcome to endure. Selective pressure during tumorigenesis can reduce or eliminate the activation of pro-death BH3-only proteins, perhaps through the deletion of key BH3-only genes or by genetic modulation of any of the poorly understood interactions functioning upstream to regulate these proteins. We refer to this as a class A block. Alternatively, the effector arm of the mitochondrial apoptotic pathway could be mutated, resulting in the reduction or elimination of BCL2-associated X protein (BAX) and BCL2-antagonist/killer (BAK). This we refer to as a class B block[72]. Finally, cancer cells may have increased expression of an inhibitor such as BCL2, myeloid cell leukaemia sequence 1 (MCL1) or a related anti-apoptotic protein. We refer to this as a class C block. Modified, with permission, from REF. 72 © Elsevier Science (2007).

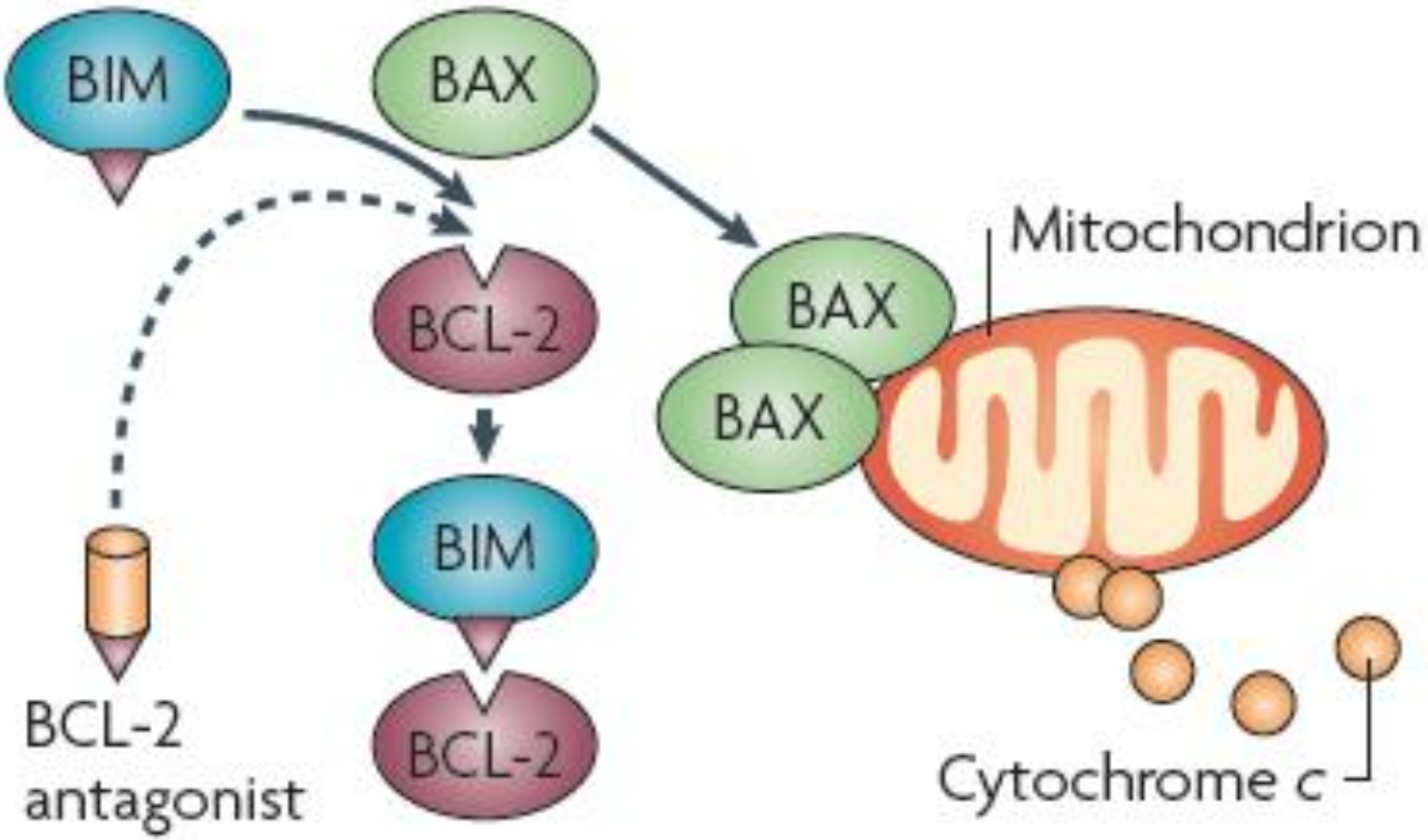
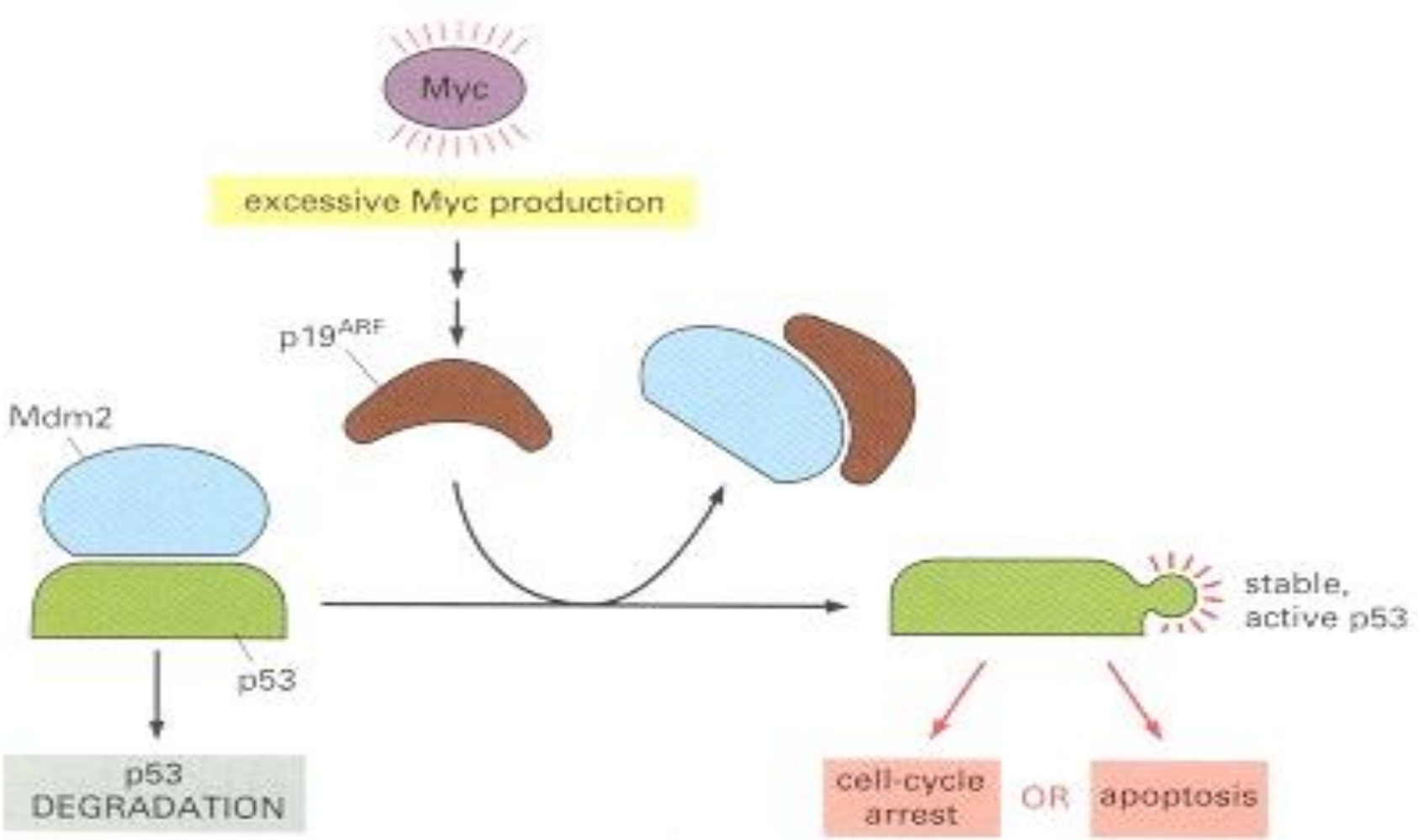

BIM
BAX
BCL-2
BIM
BCL-2
BCL-2
antagonist
BAX
BAX
Mitochondrion
Cytochrome c

Table 2 | **Clinical development of drugs targeting anti-apoptotic proteins**

Drug	Company	Clinical phase	Function	Additional comments
ABT-263	Abbott Laboratories	Phase I and I/II a clinical trials in NHL, CLL and SCLC	BH3 mimetic, targets BCL2, BCL-X_L, BCL-w	ABT-263 is an orally available compound closely related to ABT-737
Obatoclax (GX15-070)	Gemin X	Multiple phase I and phase II clincial trials in haematological malignancies and non-small cell lung cancer	BH3 mimetic	Might be a pan-inhibitor of anti-apoptotic proteins
Oblimersen (G3139)	Genta	Many clinical trials including phase III in melanoma and CLL	Antisense DNA targeting *BCL2*	None
AT-101	Ascenta Therapeutics	Phase II clinical trials in a variety of cancers	BH3 mimetic	AT-101 is the (–) enantiomer of gossypol

BH, BCL2 homology; CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; SCLC, small-cell lung cancer.

VAI TRÒ P53 TRONG APOPTOSIS



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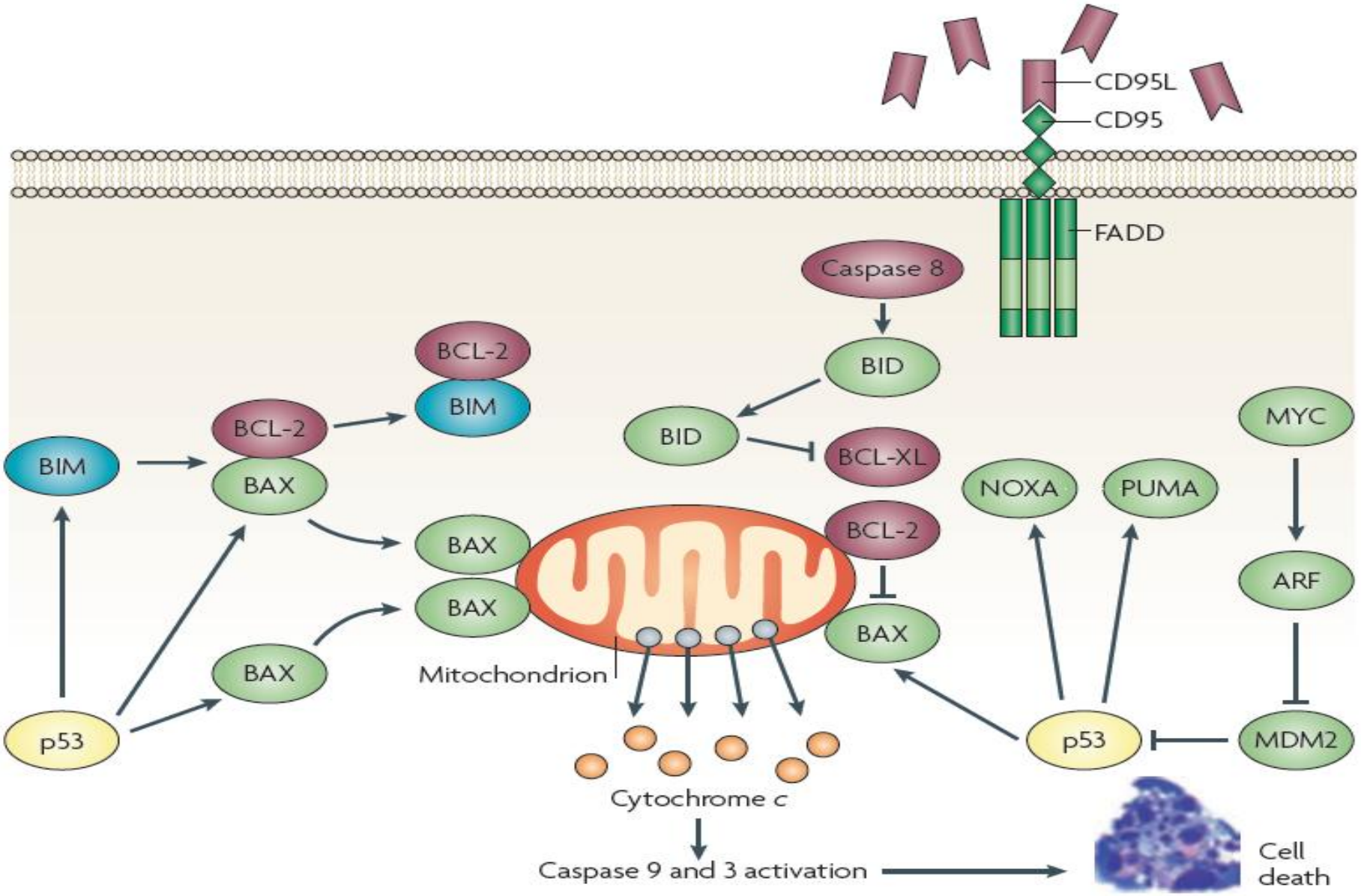


TP53 Mutations in Human Cancers: Origins, Consequences, and Clinical Use

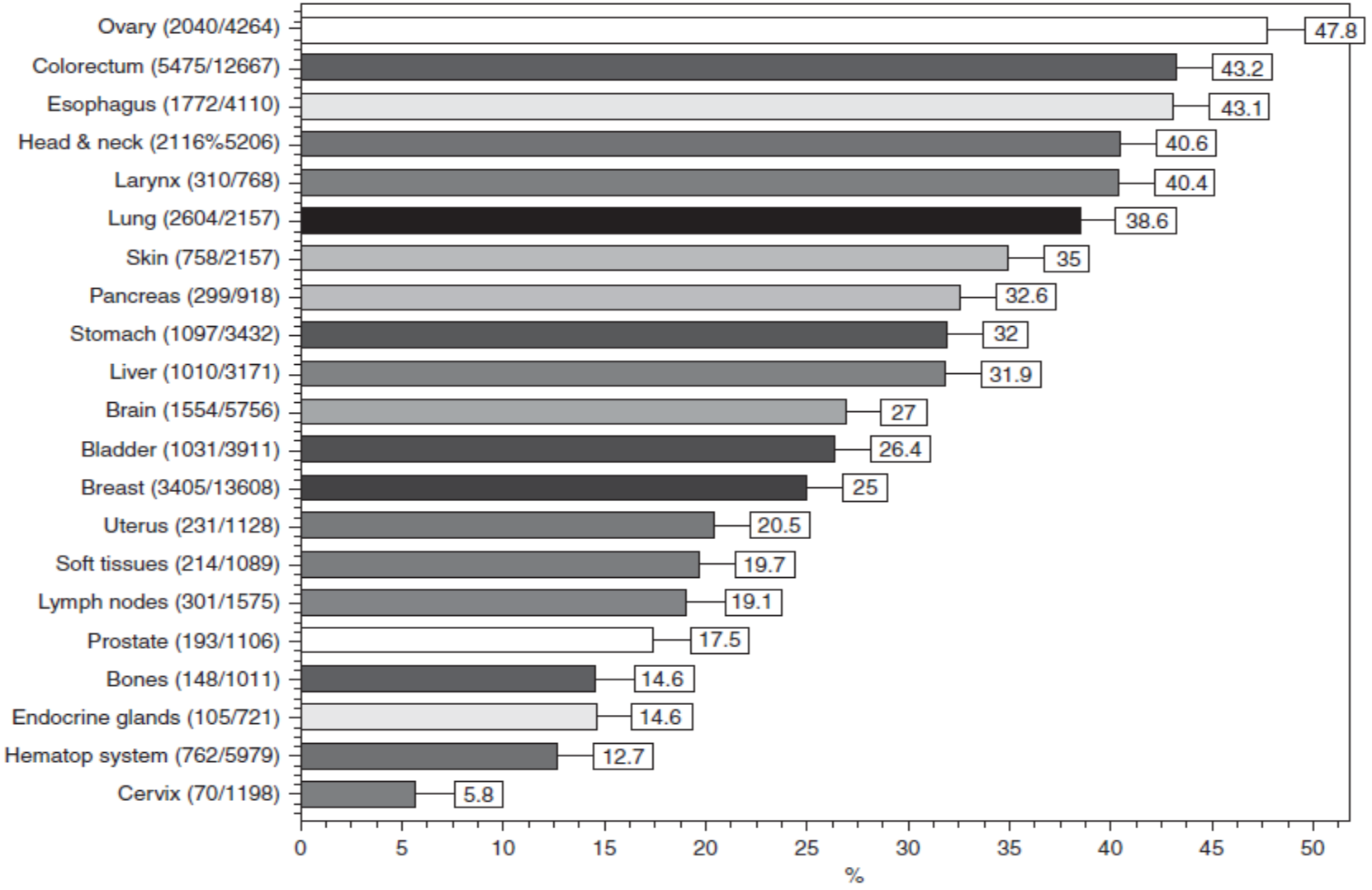
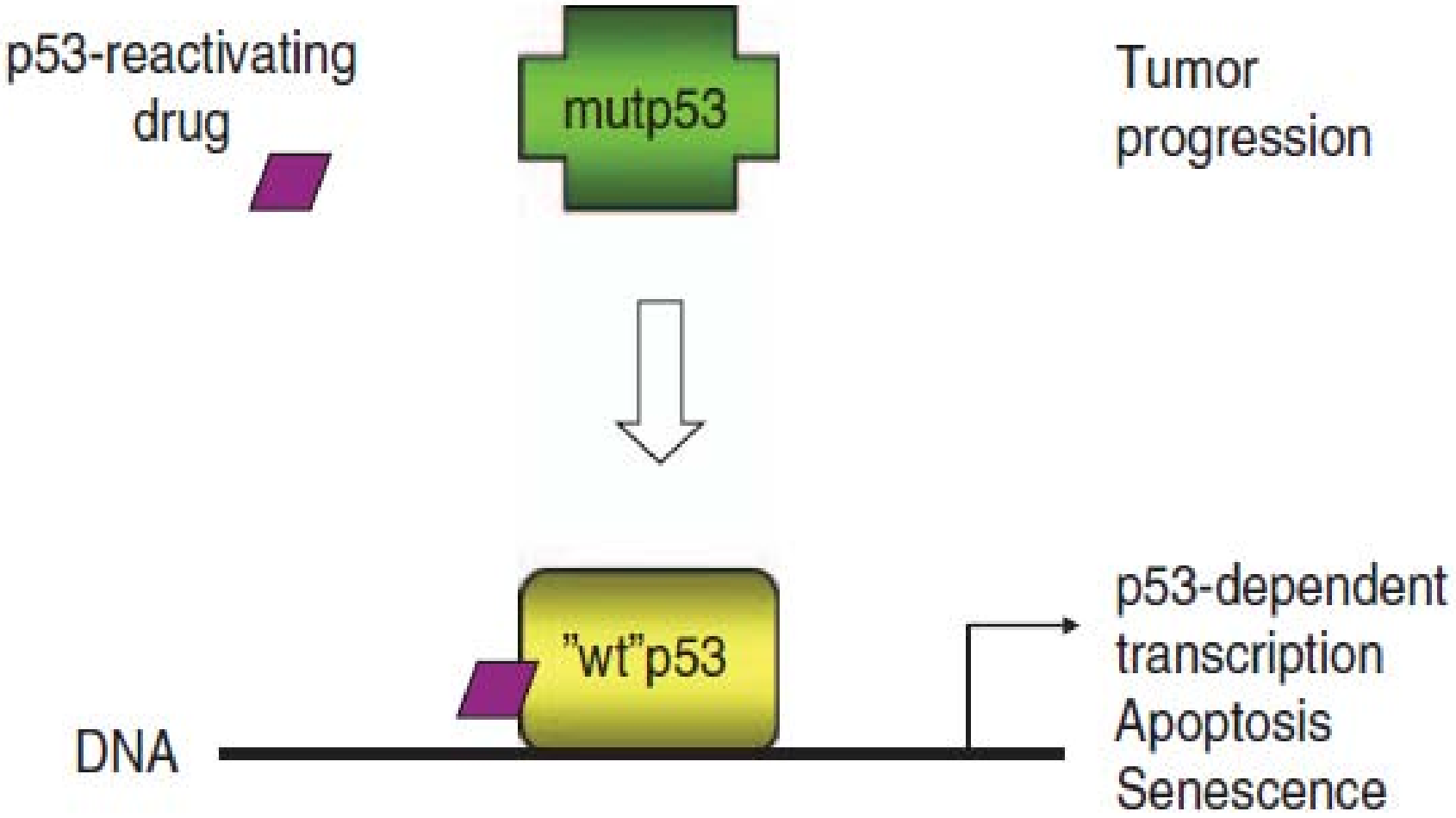


Table 2. Selective chemotherapeutic agents targeting cell death pathways

Death pathway	Protein classification	Chemotherapeutic agent	Target	Type of compound	Sponsoring organization	Stage
Apoptosis	Bcl-2	Oblimersen	Bcl-2	Antisense oligonucleotide	Genta/Aventis	Phase II/III
		SAHBs	Bcl-2 family	Peptidomimetic	Harvard University	Preclinical
		ABT-737	Bcl-2/Bcl-xL	Small compound	Abbott	Preclinical
		Gossypol	Bcl-2	Small compound	NCI/Ascenta	Phase I
	IAP	Compound 3	IAPs	Small compound	University of Texas Southwestern	Preclinical
		AEG 35156/ GEM640	XIAP	Antisense oligonucleotide	Aegera/Hybridon	Phase I (outside U.S.)
		Polyphenylureas	XIAP/caspase-3, -7	Small compound	The Burnham Institute	Preclinical
	p53	Nutlins	p53/MDM2	Small compound	Hoffman-La Roche	Preclinical
	Death receptors	TRAIL	DR4/DR5	Recombinant protein	Genentech/Amgen	Phase I
		HGS-ETR1	DR4	Agonistic mAb	Human Genome Sciences	Phase II
		HGS-ETR2	DR5	Agonistic mAb	Human Genome Sciences	Phase II
		TNF-α	TNFR	Recombinant protein		FDA approved, limb perfusion
		CDDO	FLIP	Small compound	Dartmouth College/Reata	Preclinical
Necrosis		PDT	Metabolism, ROS, Ca^{2+}			Clinical
	PARP	DNA alkylating agents	DNA damage, metabolism			Clinical
		β-Lapachone	Metabolism, ROS, Ca^{2+}	Natural compound		Preclinical
Mitotic catastrophe	Mitosis	SB-715992	KSP/Eg5	Small compound	Cytokinetics/GSK	Phase II
		UCN-01	Chk1	Small compound	NCI	Phase I/II
		CEP-3891	Chk1	Small compound	Cephalon	Preclinical
		SB-218078	Chk1	Small compound	GSK	Preclinical
		A-641397	Chk1	Small compound	Abbott	Preclinical
Senescence	Telomerase	GRN163L	hTR	Antisense oligonucleotide		Preclinical

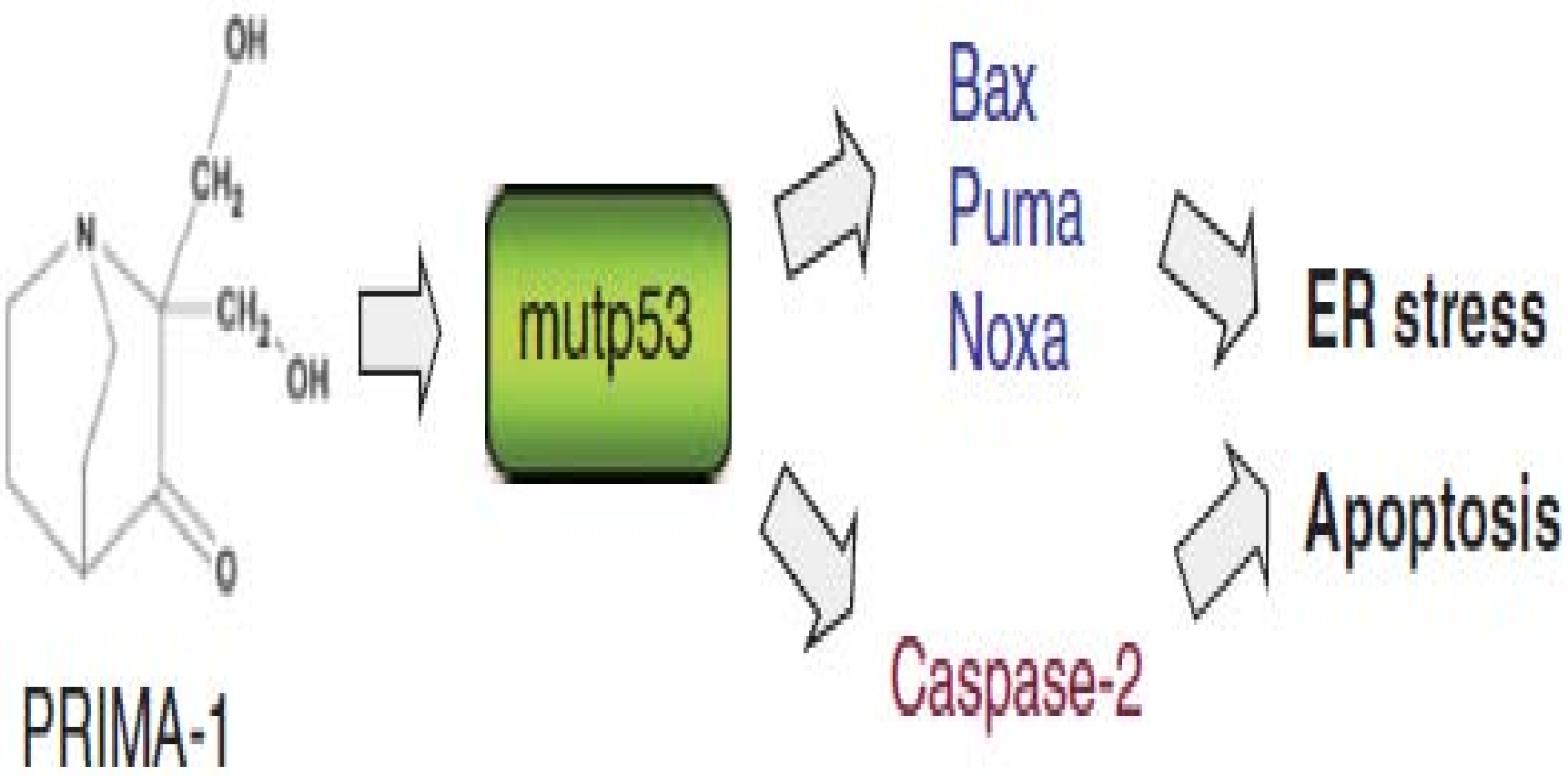
(Ricci MS, ***The Oncologist*** 2006)

CHIẾN LƯỢC ĐIỀU TRỊ DỰA TRÊN P53

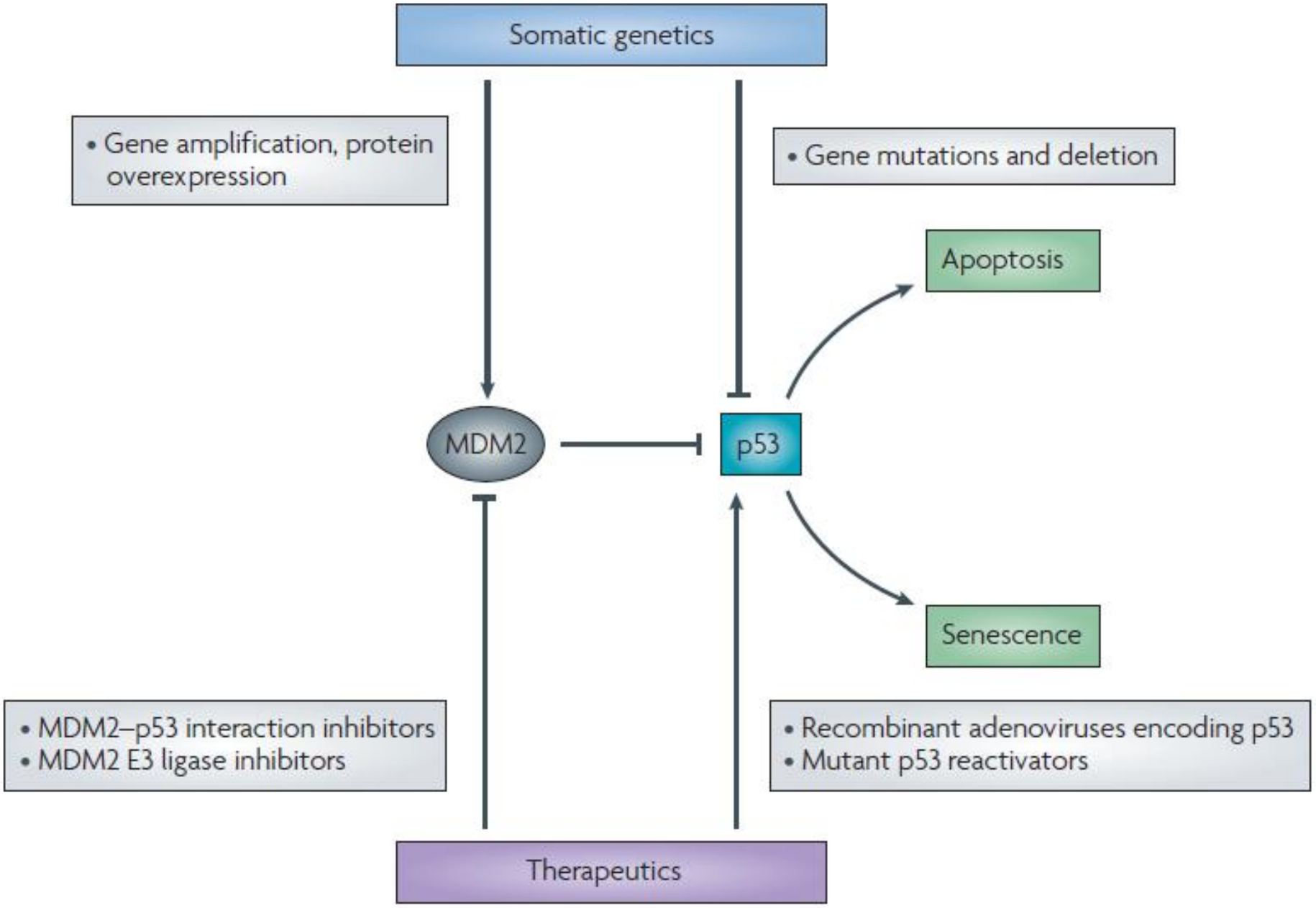


(Wiman KG, Oncogene 2010)

CƠ CHẾ TÁC ĐỘNG CỦA PRIMA-1



(PRIMA-1: P53 reactivation and induction of massive apoptosis)


Somatic genetics
• Gene amplification, protein overexpression
• Gene mutations and deletion
Apoptosis
MDM2
p53
Senescence
• MDM2–p53 interaction inhibitors
• MDM2 E3 ligase inhibitors
• Recombinant adenoviruses encoding p53
• Mutant p53 reactivators
Therapeutics