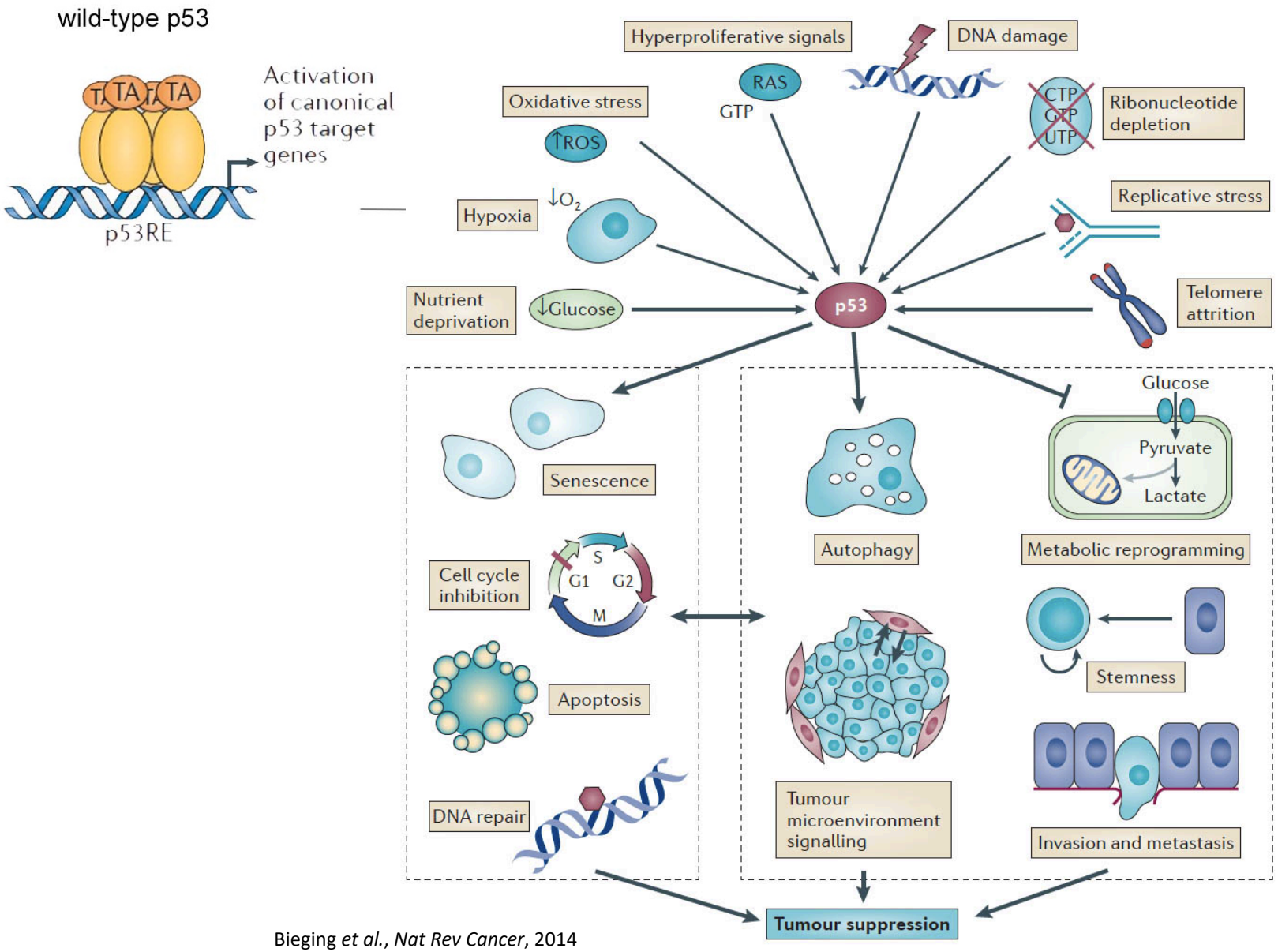
Corso di Biologia Cellulare del Cancro AA 2019-2020

HALLMARK #4:
EVASIONE DAI MECCANISMI ONCOSOPPRESSIVI INTRINSECI

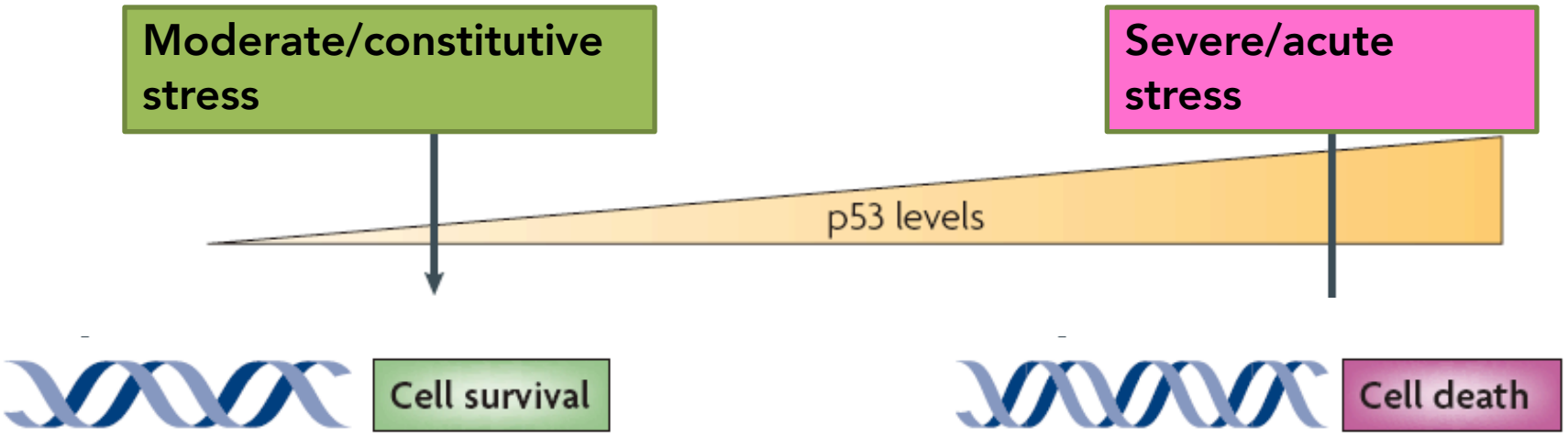
RESISTENZA ALLA MORTE CELLULARE

p53 induce diverse risposte cellulari oncosoppressive…



Bieging *et al.*, *Nat Rev Cancer*, 2014

…a seconda dello stimolo e del contesto cellulare



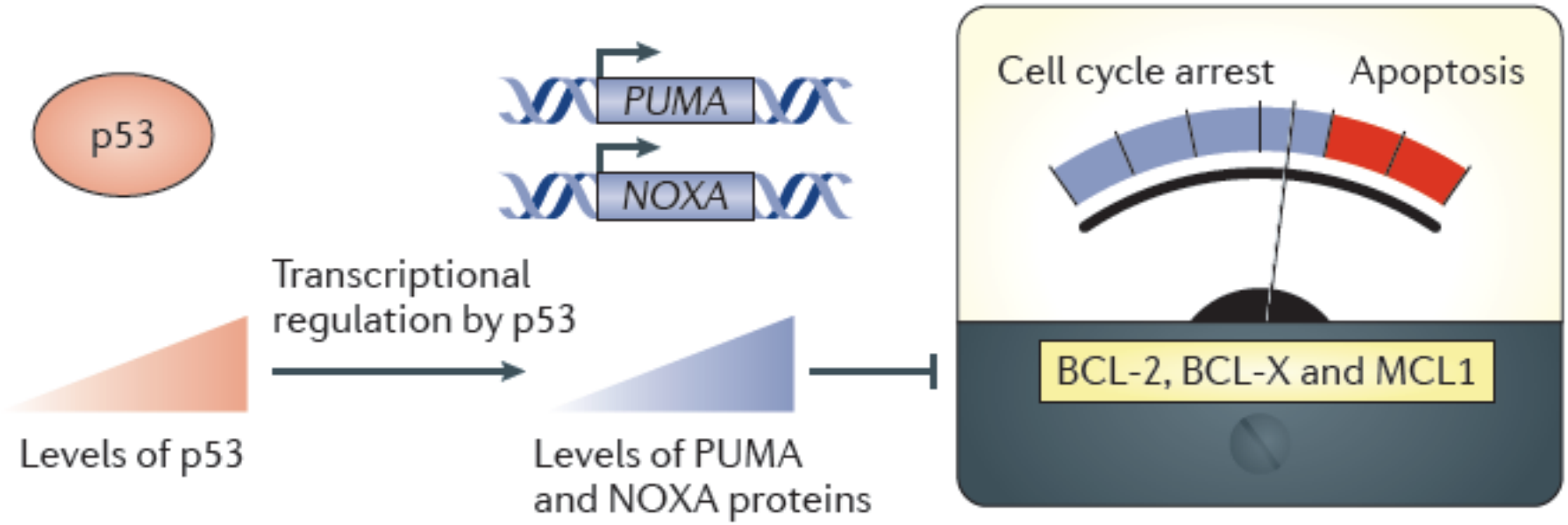
PROTECTION/REPAIR
Transient cell cycle arrest
Anti-oxidant functions
DNA repair
Cell metabolism

TUMOR PREVENTION
LONGEVITY
FERTILITY

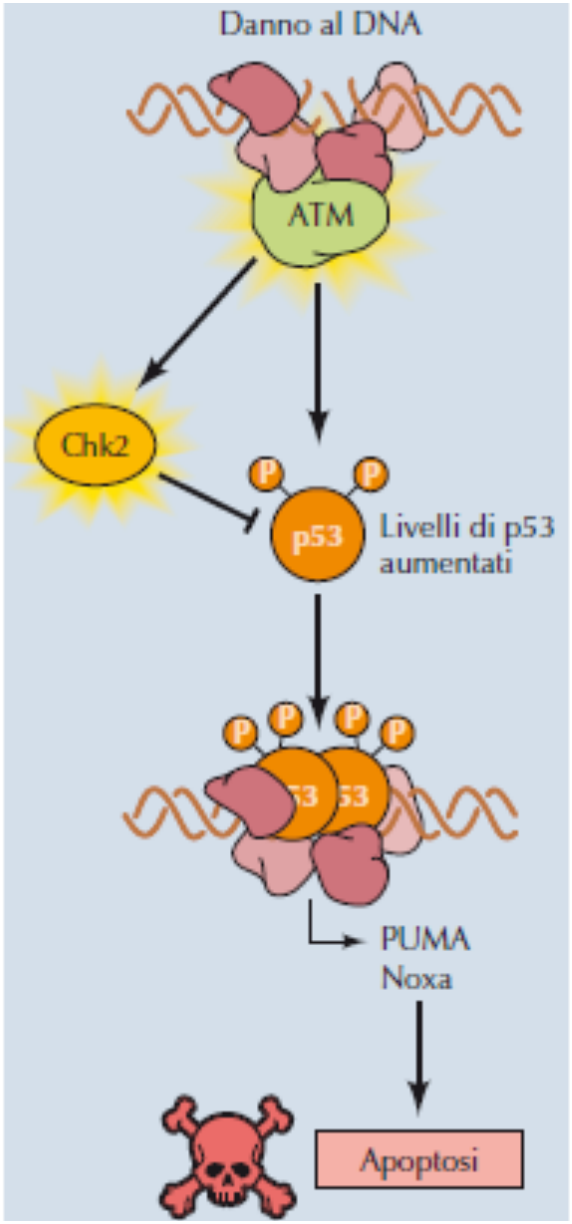
ELIMINATION OF DAMAGED CELLS
Apoptosis/autophagy
Senescence
Differentiation

TUMOR SUPPRESSION
TOXICITY OF THERAPIES
AGING
DEVELOPMENT

L'induzione dell'apoptosi dipende dall'attivazione di uno specifico programma trascrizionale da parte di p53



La decisione di indurre l'apoptosi dipende dal tipo ed entità dello stress e dal contesto cellulare



Severe/persistent DNA damage

Activation of specific enzymes

p53 threshold levels

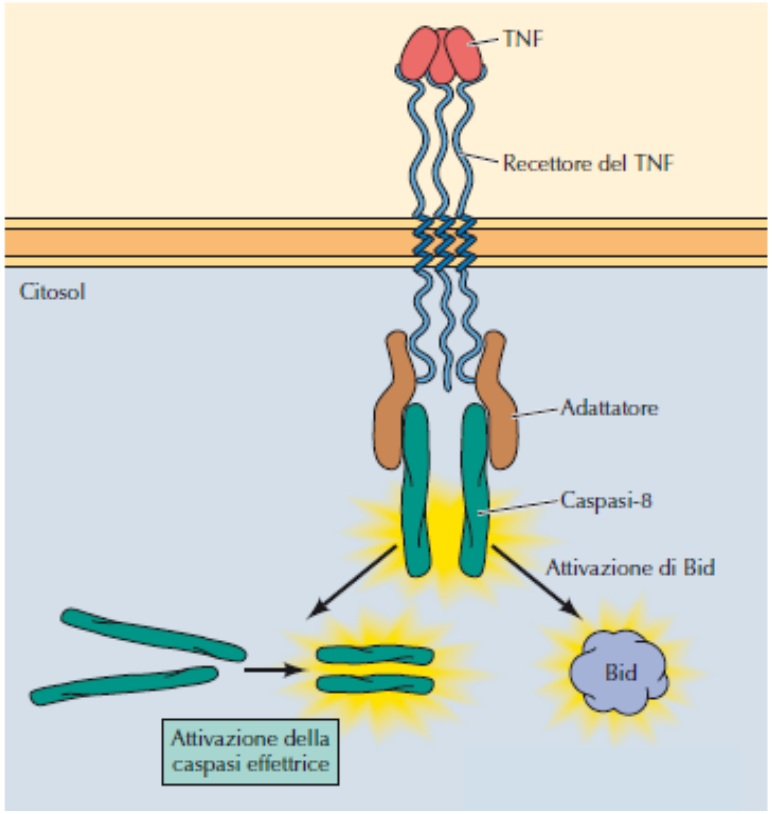
Code of PTMs

Interaction with cofactors

Le strategie terapeutiche mirate all'induzione di morte cellulare devono essere mirate ai meccanismi di morte cellulare attivi nelle cellule tumorali

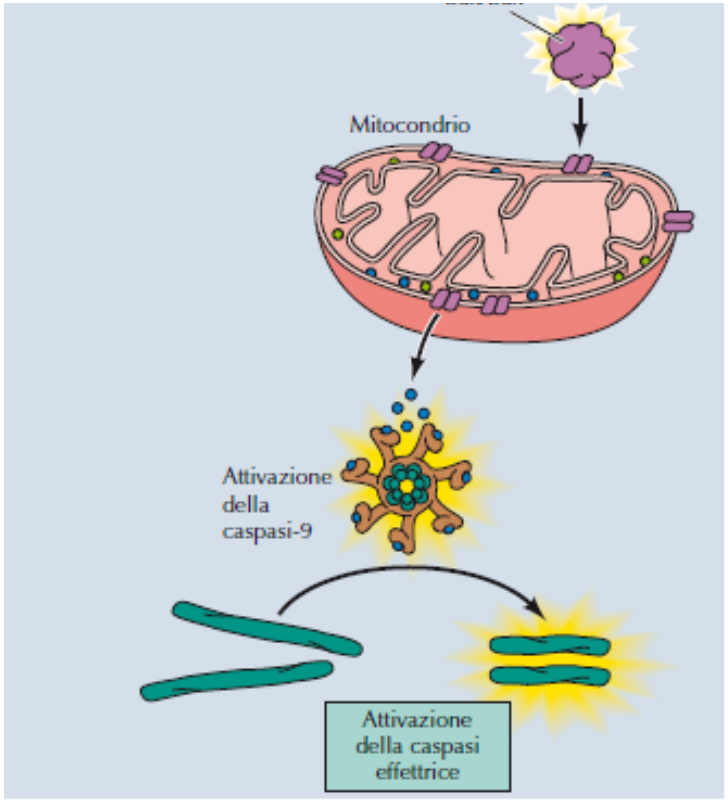
Apoptosi: via estrinseca e via intrinseca

Segnale di morte extracellulare



Es. TRAIL

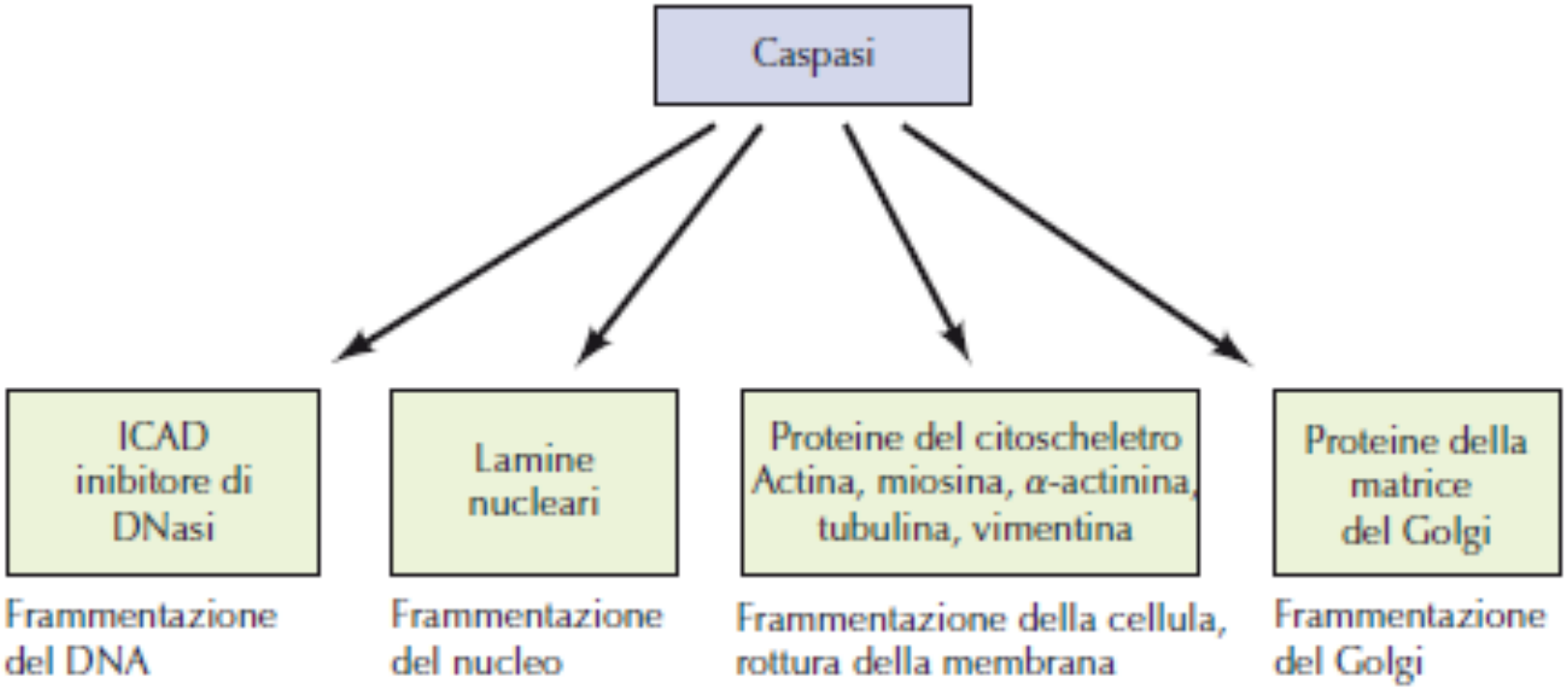
Segnale di morte intrinseco



Es.
Danno al DNA non riparabile
ER stress cronico,
Ipossia
Stress metabolico

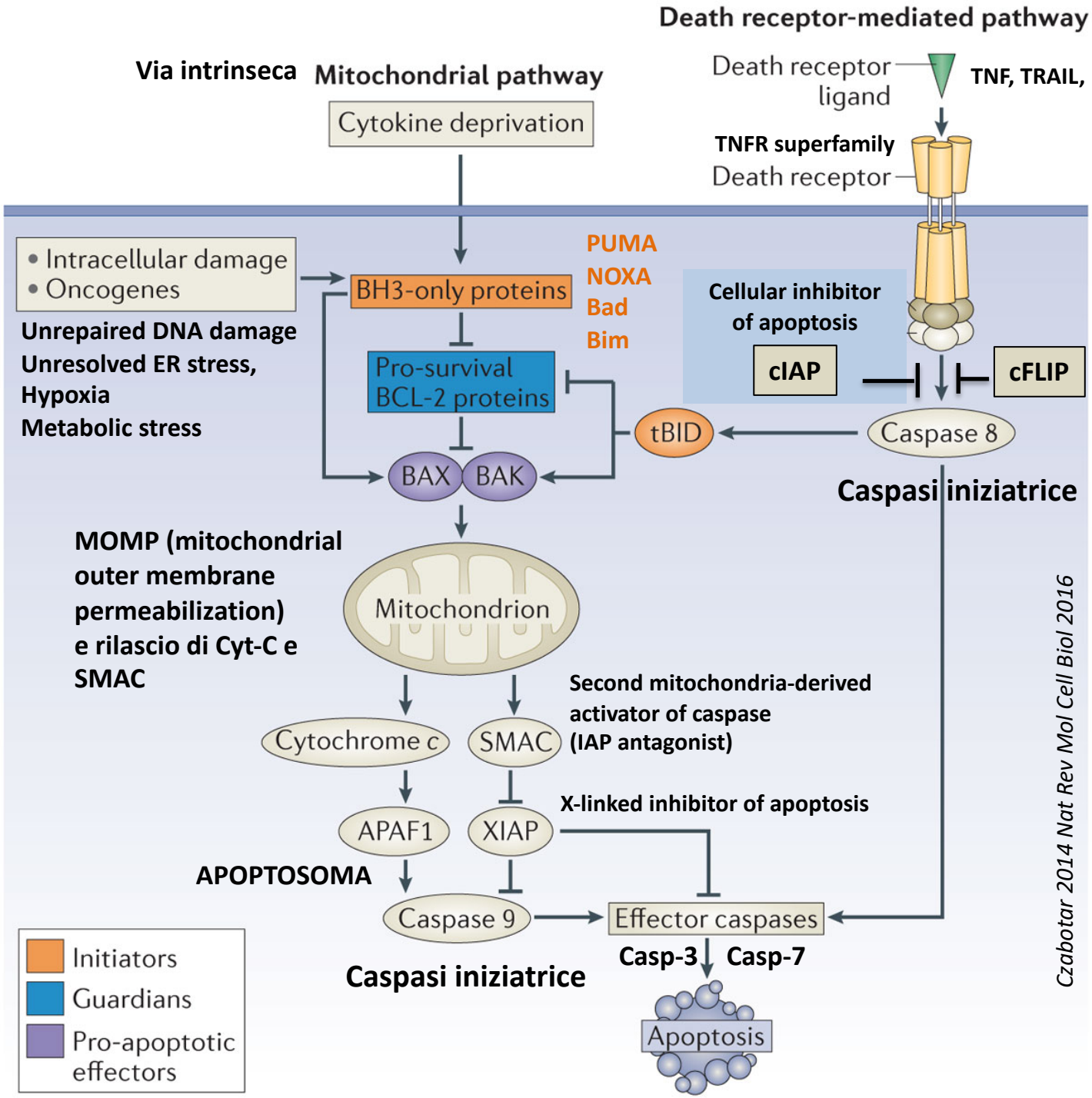
Effettori dell'apoptosi: le CASPASI

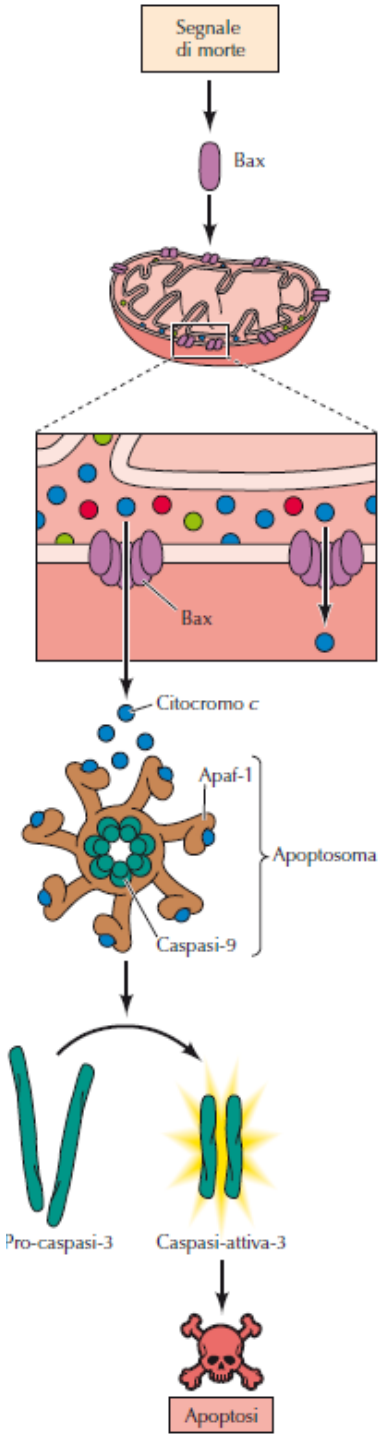
Cistein-proteasi che tagliano a monte di un residuo di Asp



Regolatori dell'apoptosi

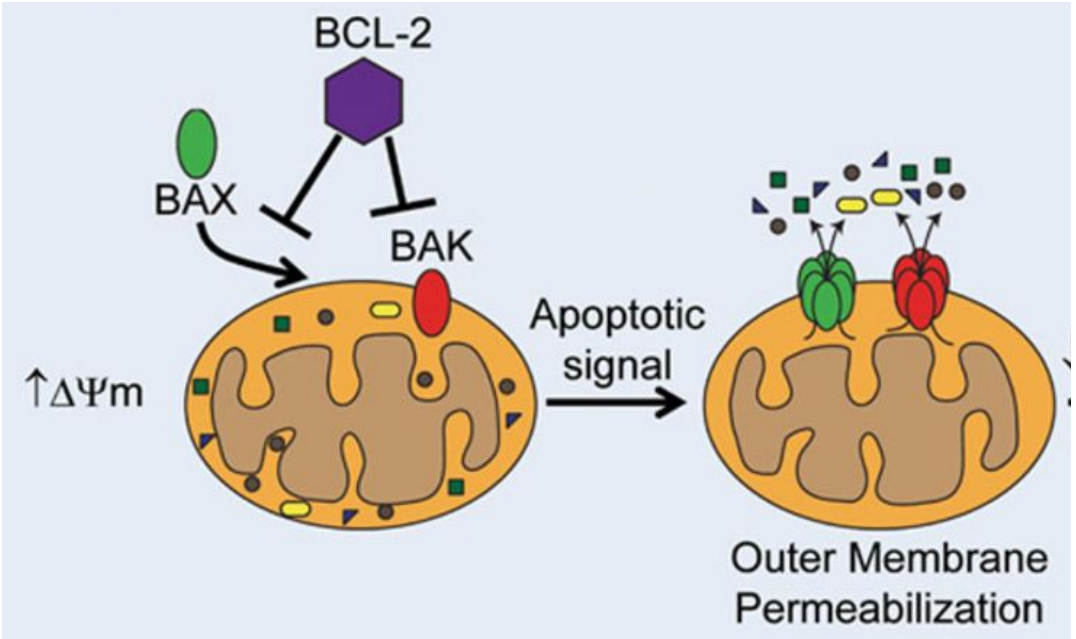
- Membri della famiglia di Bcl-2 (B-cell lymphoma 2)
- Inhibitori dell' apoptosi (IAPs)
- Antagonisti di IAP (SMAC/DIABLO)


Death receptor-mediated pathway
Via estrinseca
Via intrinseca
Mitochondrial pathway
Death receptor ligand
TNF, TRAIL, FASL
Cytokine deprivation
TNFR superfamily Death receptor
• Intracellular damage
• Oncogenes
Unrepaired DNA damage
Unresolved ER stress,
Hypoxia
Metabolic stress
BH3-only proteins
PUMA
NOXA
Bad
Bim
Cellular inhibitor of apoptosis
cIAP
cFLIP
Pro-survival BCL-2 proteins
tBID
Caspase 8
BAX
BAK
Caspasi iniziatrice
MOMP (mitochondrial outer membrane permeabilization) e rilascio di Cyt-C e SMAC
Mitochondrion
Second mitochondria-derived activator of caspase (IAP antagonist)
Cytochrome c
SMAC
X-linked inhibitor of apoptosis
APAF1
XIAP
APOPTOSOMA
Caspase 9
Effector caspases
Casp-3
Casp-7
Caspasi iniziatrice
Apoptosis
Initiators
Guardians
Pro-apoptotic effectors
Czabotar 2014 Nat Rev Mol Cell Biol 2016

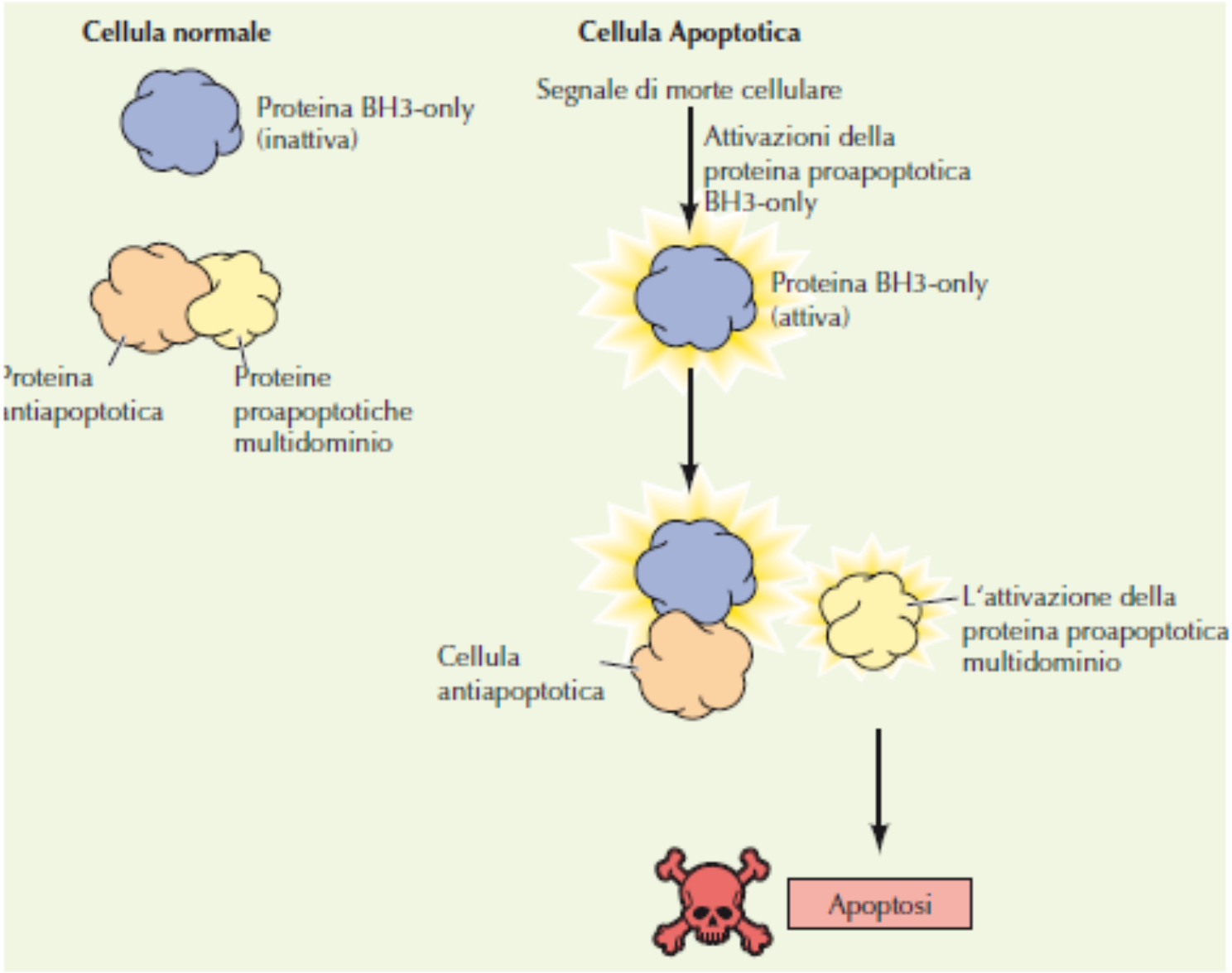


Le proteine proapoptotiche multidominio:

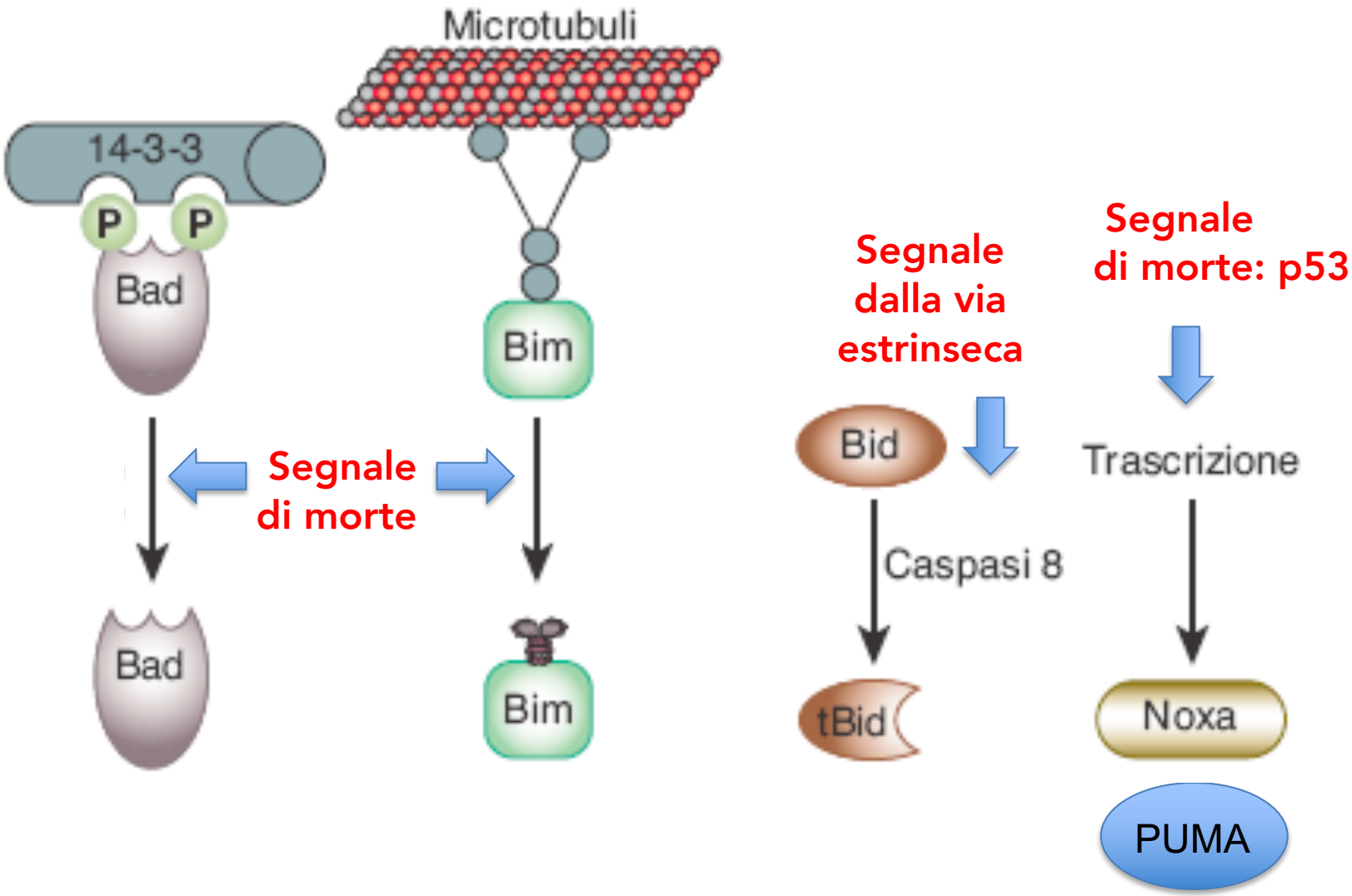
EFFETTORI della permeabilizzazione mitocondriale (MOMP)



Interazioni regolatorie tra i membri della famiglia di Bcl-2



L'attivazione della via intrinseca è mediata dalle piccole proteine BH3-only



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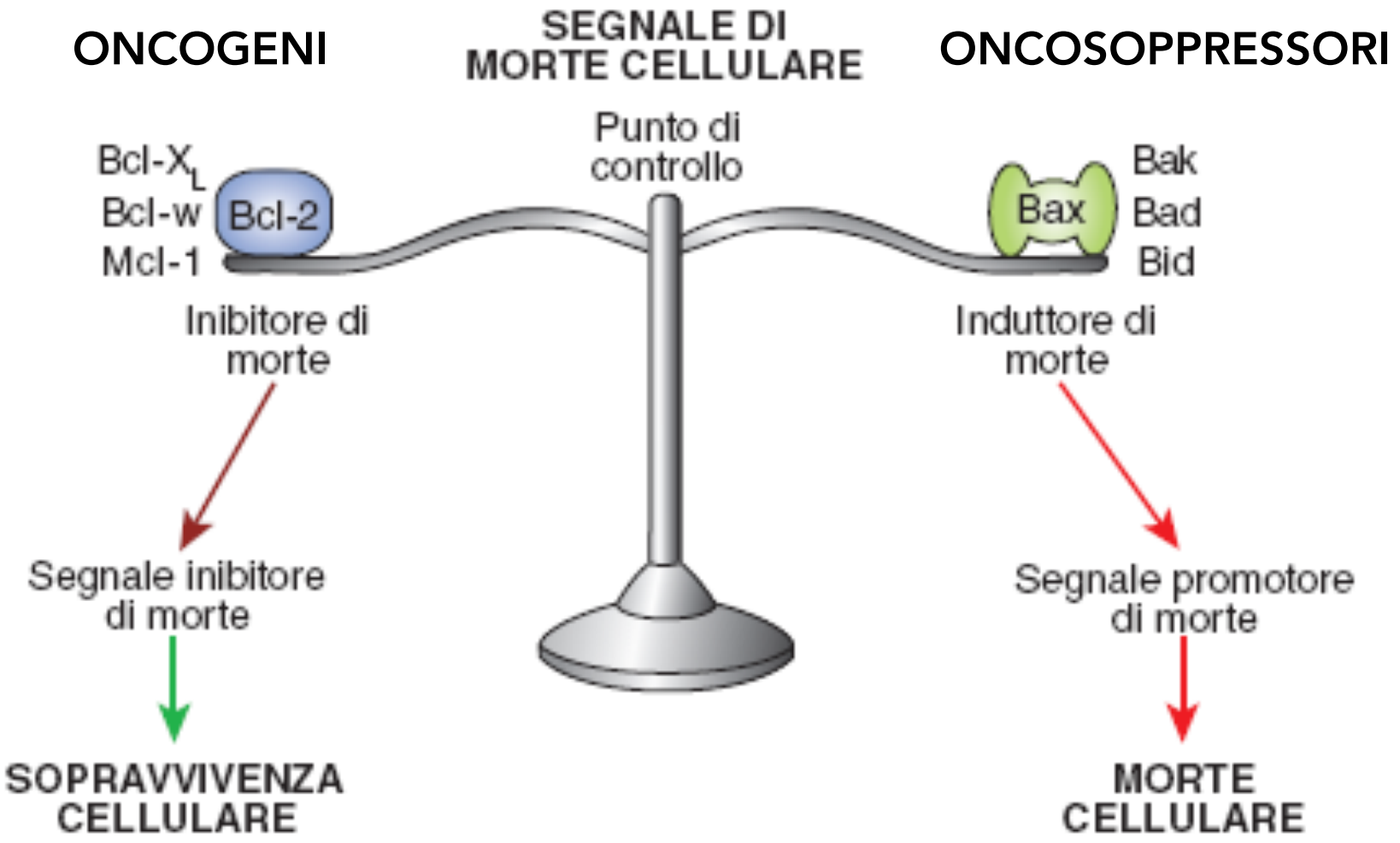
I membri della famiglia di Bcl2 regolano l'equilibrio tra sopravvivenza e morte cellulare



Regolatori dell'apoptosi

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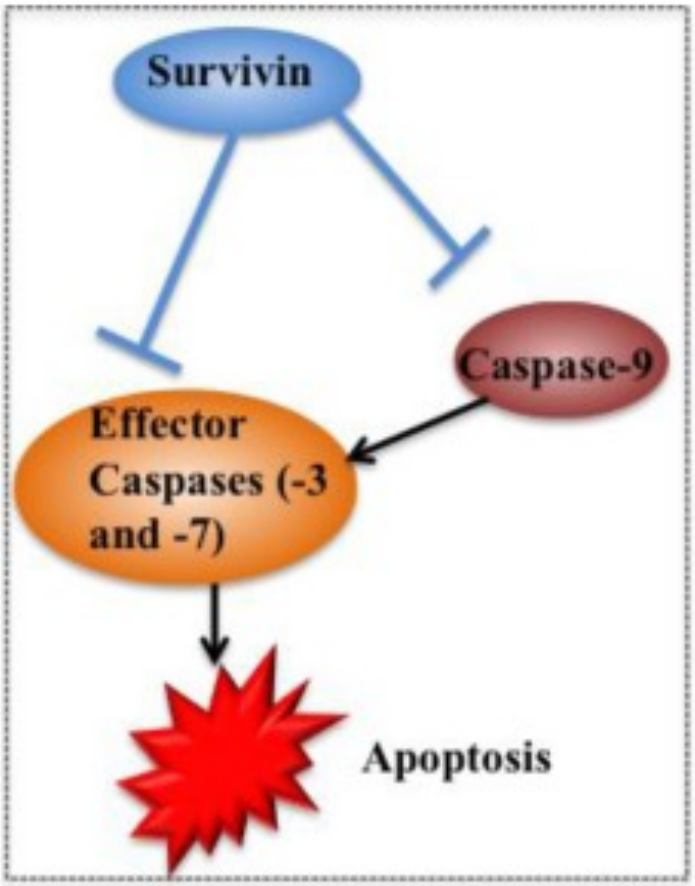
Inhibitor of apoptosis proteins IAPs

NAIP
cIAP1
cIAP2
XIAP
MLIAP
ILP2
Survivin
Apollon

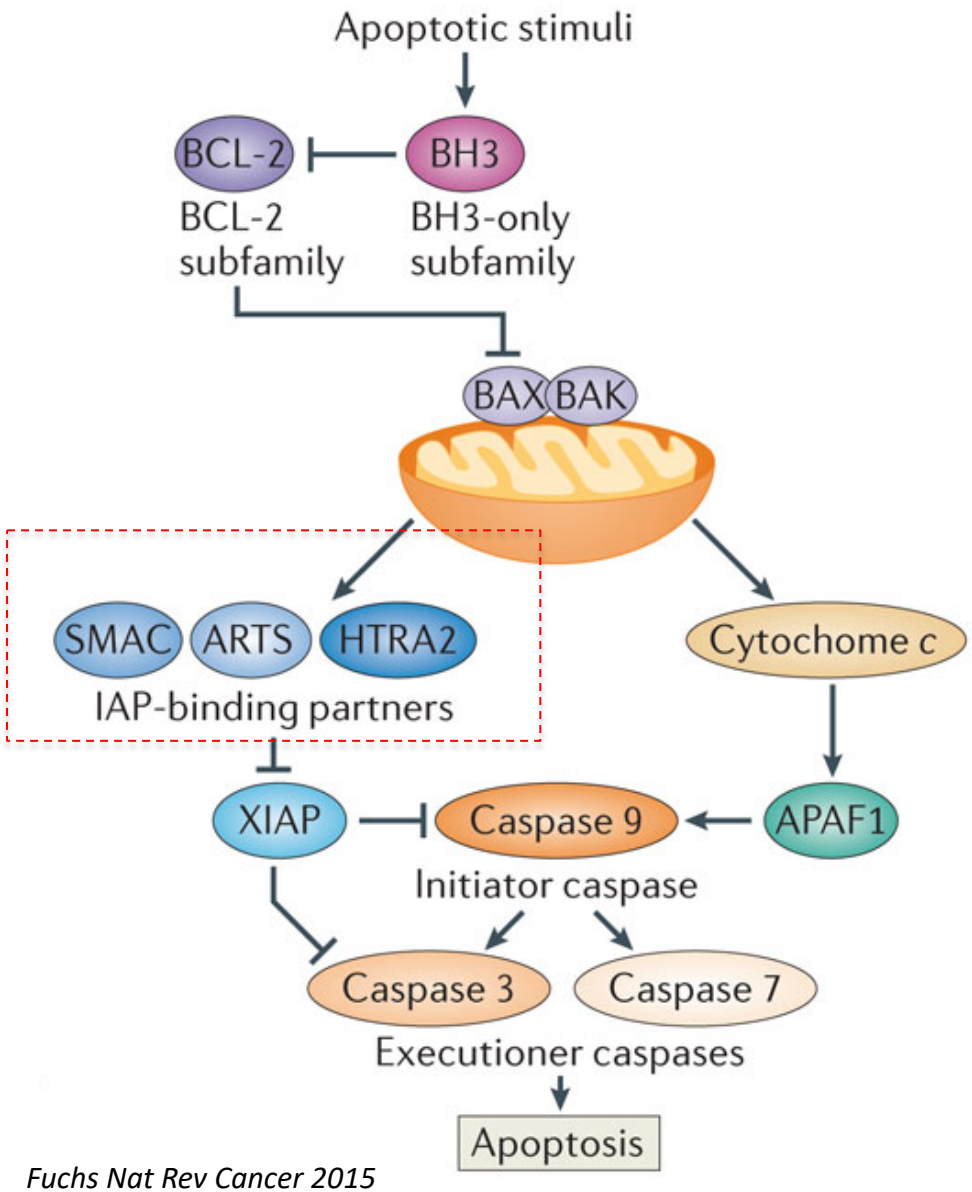


IAPs legano direttamente le CASPASI

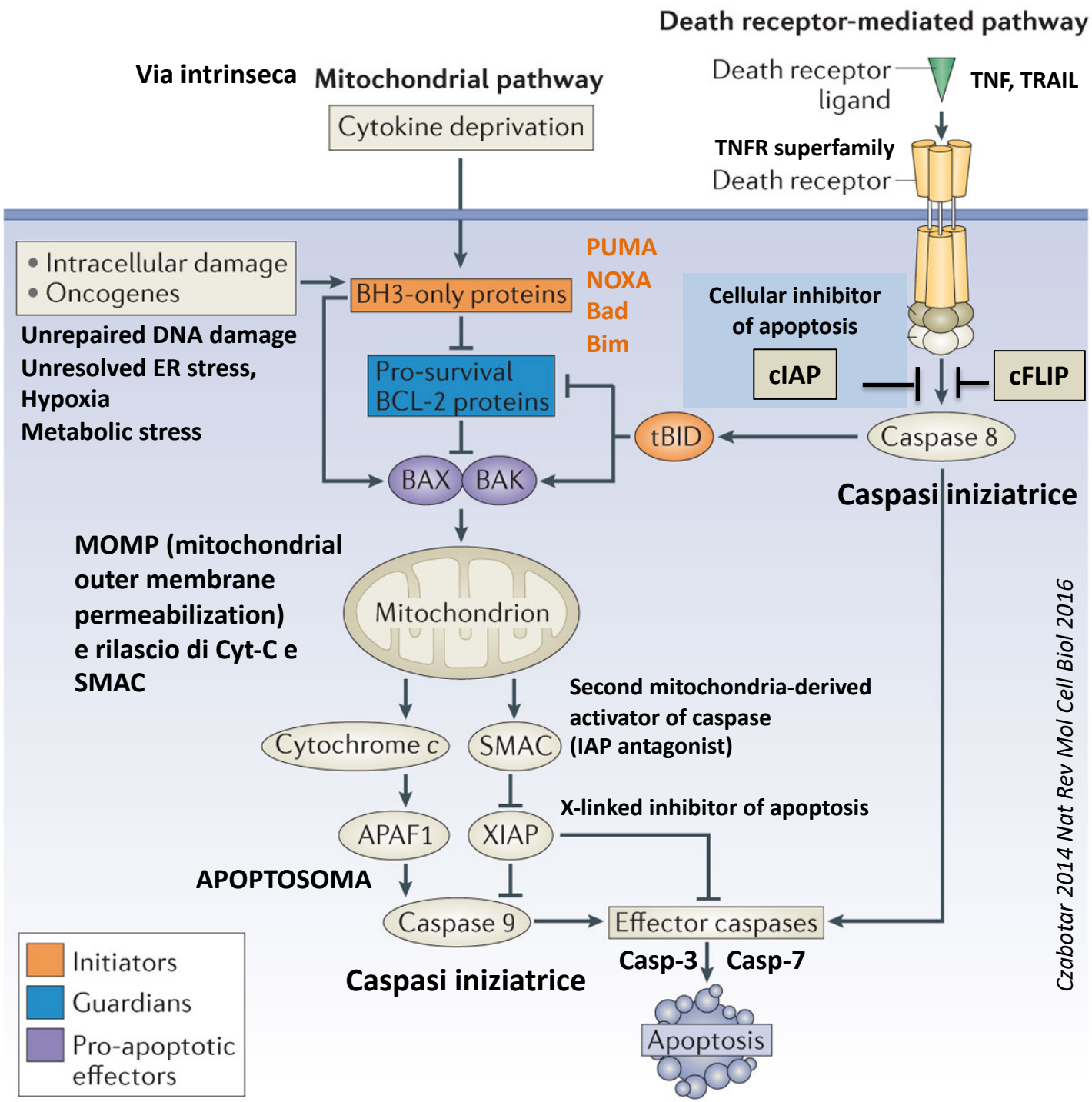
RING (really interesting new gene) domain conferisce attività ubiquitin protein ligase (E3) causando degradazione di proteine proapoptotiche

IAP antagonists

IAP antagonists



Fuchs Nat Rev Cancer 2015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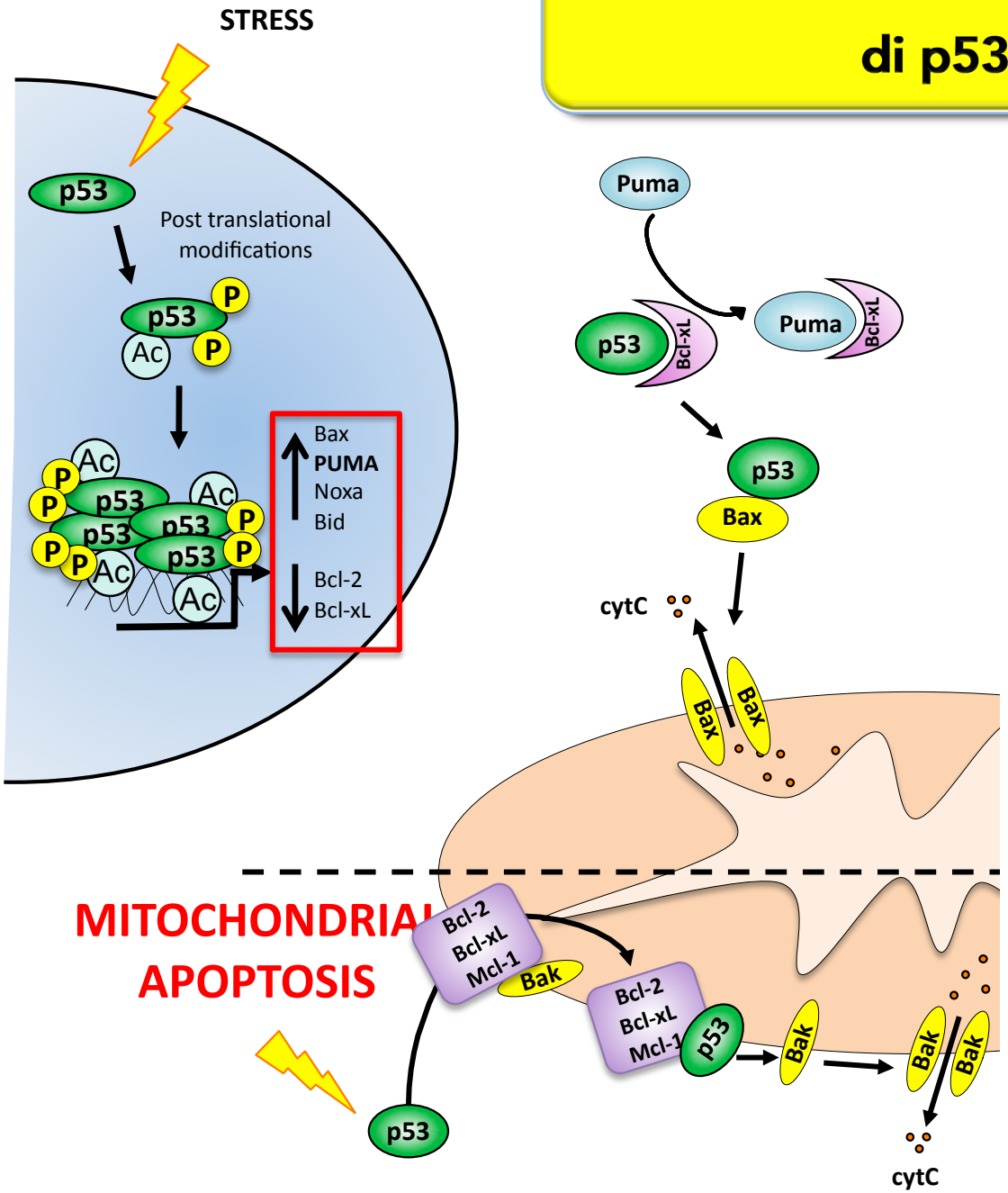
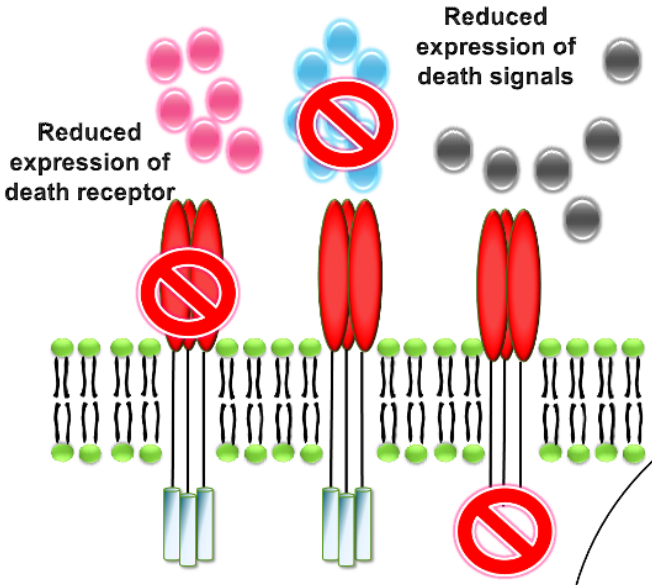
Ruoli nucleari ed extra-nucleari di p53 nell'apoptosi



Meccanismi di evasione dall'apoptosi



Impaired receptor signaling pathway

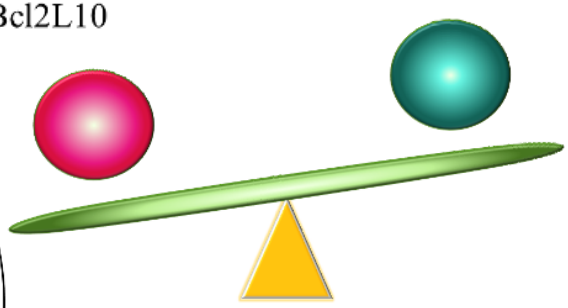
Overexpression of antiapoptotic proteins

Group I
Bcl-2, Bcl-xL, Mcl-1, Bcl-w, A1/BF-1, BclB/Bcl2L10

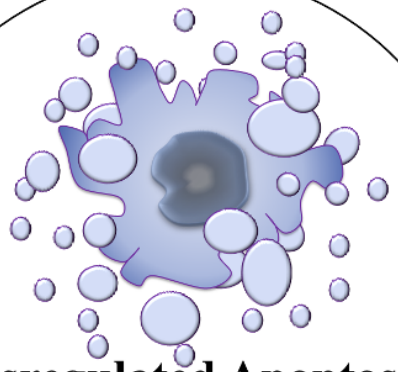
Underexpression of proapoptotic proteins

Group II
Bid, Bim, Puma, Noxa,Bad, Bmf, Hrk, Bik

Group III
Bax, Bak, Bok/Mtd



Disrupted balance of Bcl-2 family of proteins



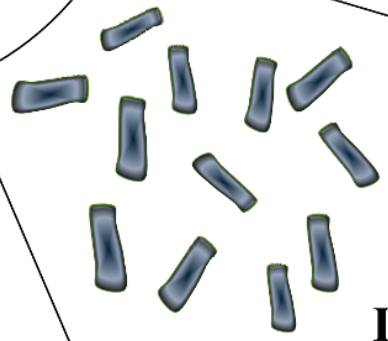
Dysregulated Apoptosis & Cancer

Wong J Exp Clin Cancer Res 2011

Defects/ mutations in p53

Apaf-1 repression

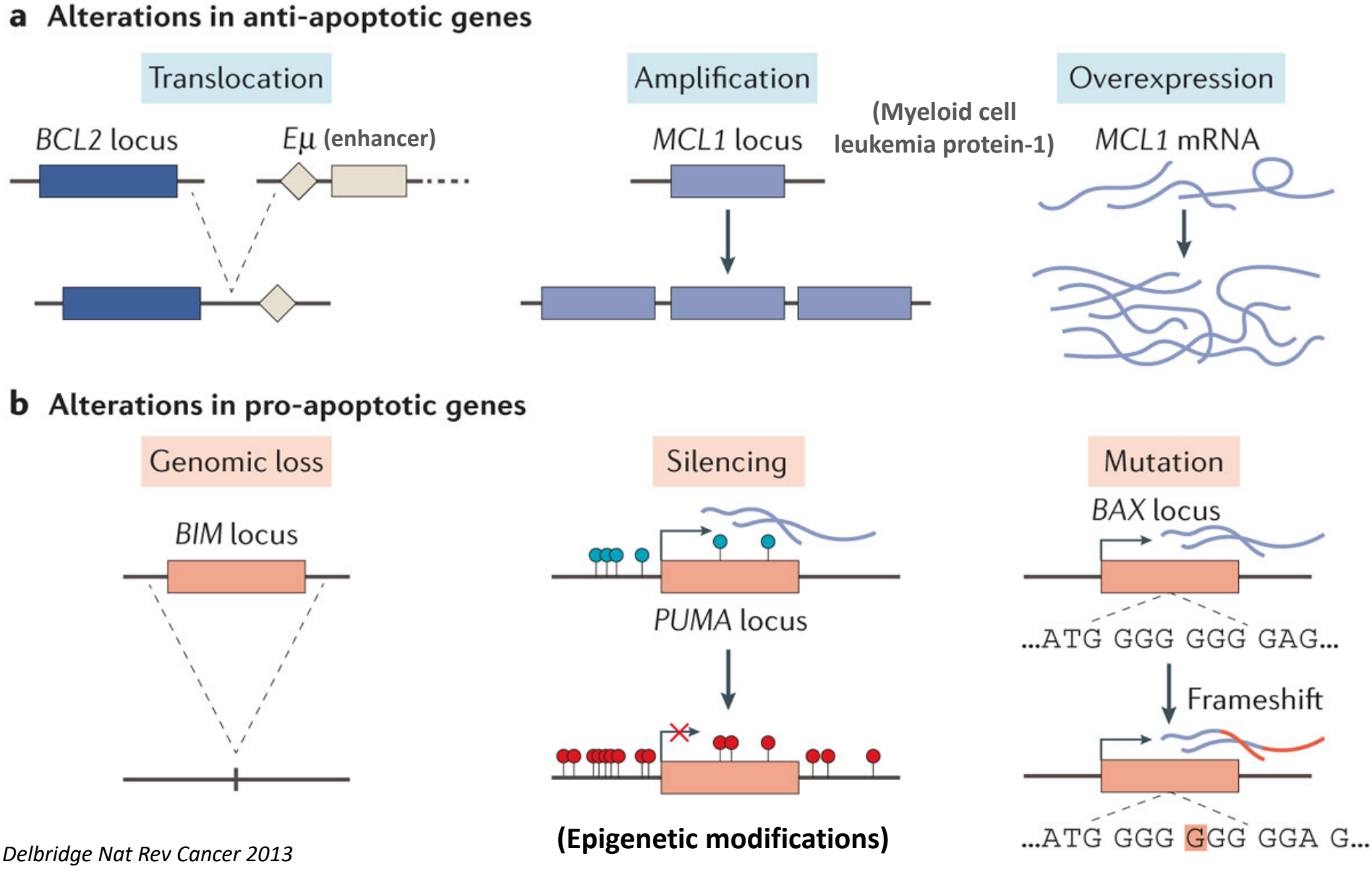
Reduced expression of caspases



XIAP

Increased expression of IAPs

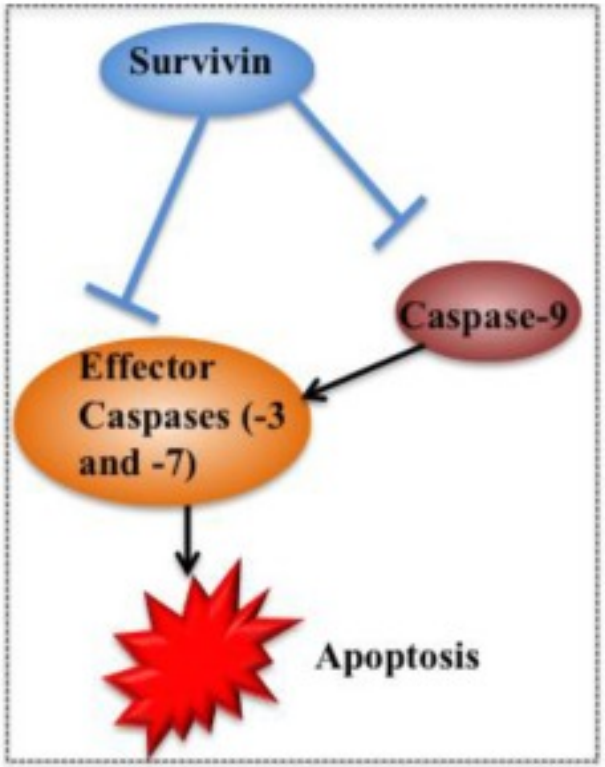
Deregolazione dei membri della famiglia di Bcl2

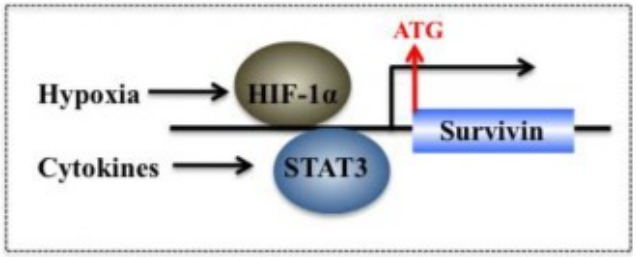


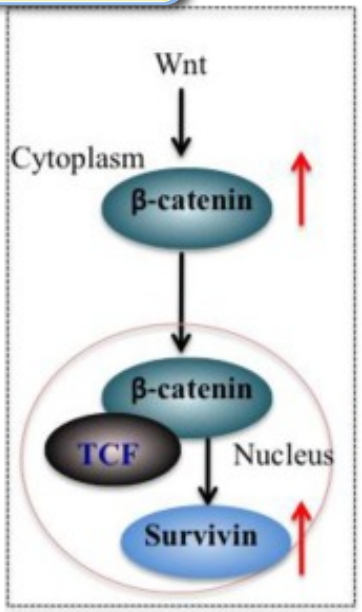
Delbridge Nat Rev Cancer 2013

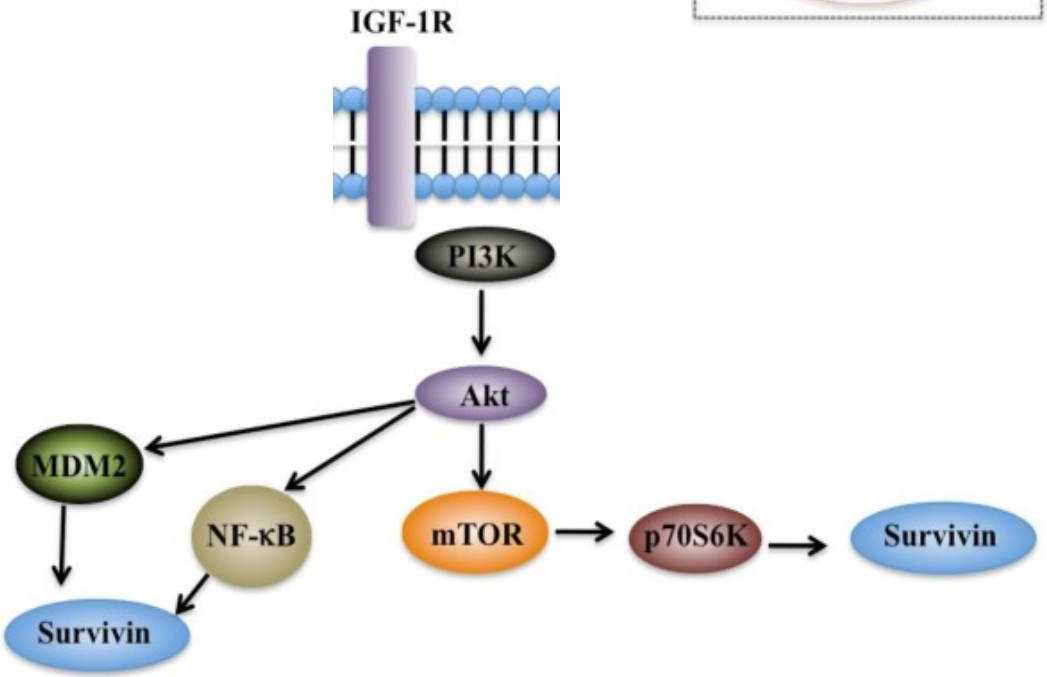
Deregolazione della survivina

È indotta in molti tumori da stress e pathways oncogeniche



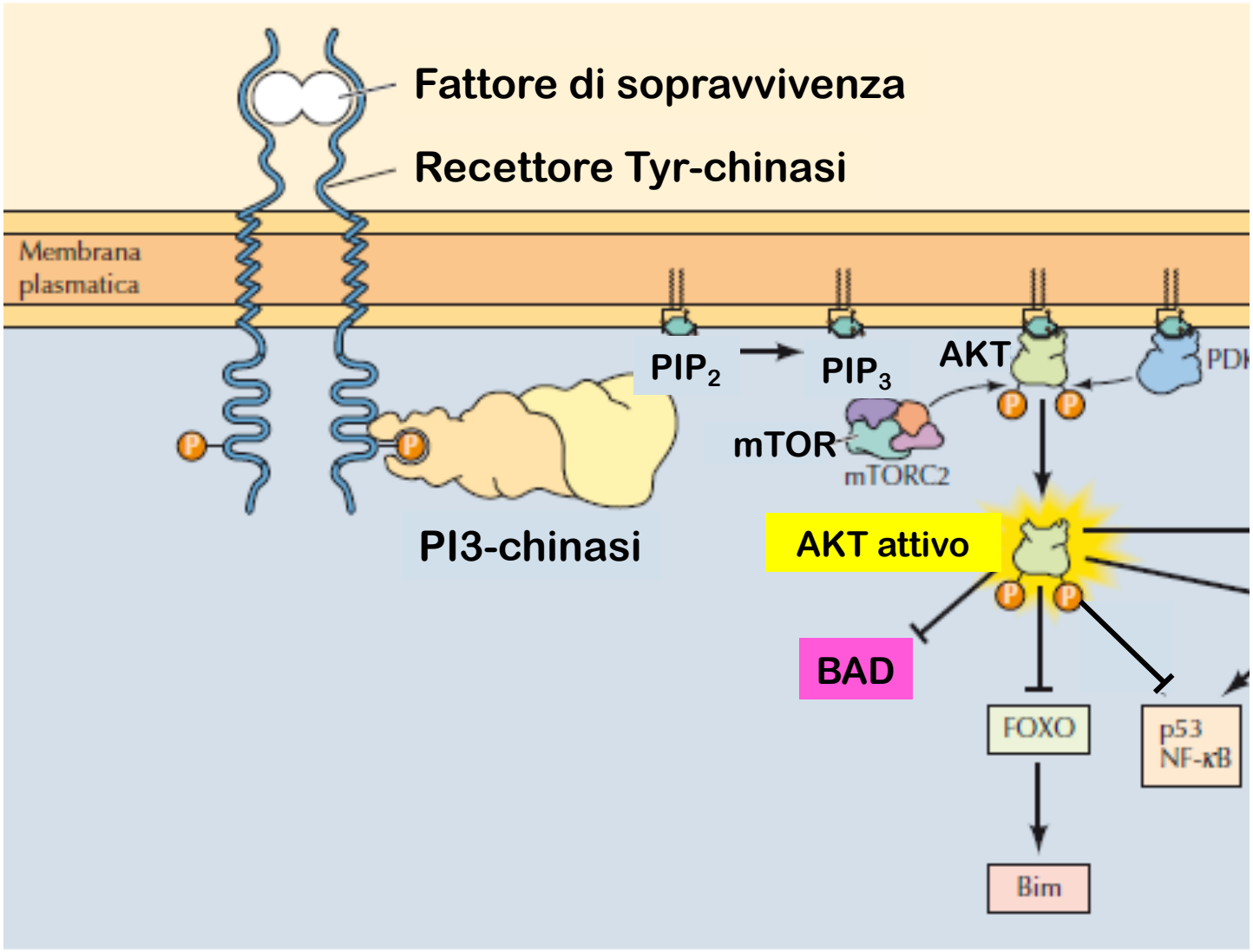






Chen J Cancer 2016

Segnali di sopravvivenza cellulare inibiscono l'apoptosi

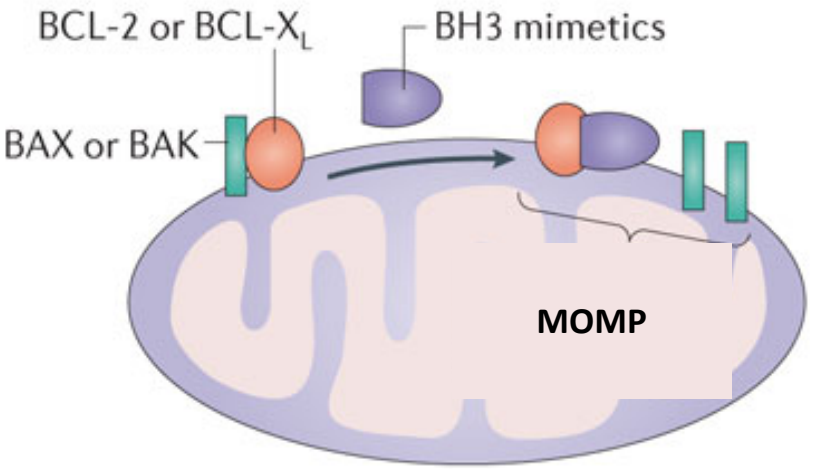


Terapie mirate per l'induzione di apoptosi

TRAIL receptor agonists

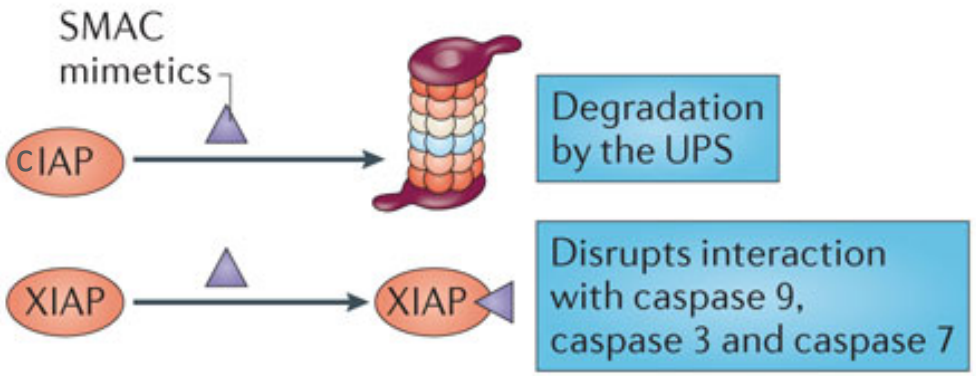
Bcl-2 targeted chemotherapeutics

BH3 mimetics



IAP antagonist molecules

SMAC mimetics



Holohan Nat Rev Cancer 2013

Farmaci contro Bcl2

Table 1 | **BH3-mimetics undergoing clinical trials for cancer indications**

BH3-mimetic	Alternative name	Targets	Therapy	Indication	Clinical trial
ABT-199	Venetoclax	BCL-2	Single agent	Chronic lymphocytic leukaemia	Phase III
				Acute myeloid leukaemia	Phase I/II
				Diffuse large B cell lymphoma	Phase I
				Follicular lymphoma	Phase I
				Lymphoma	Phase I
				Mantle cell lymphoma	Phase I
				Multiple myeloma	Phase I
				Non-Hodgkin lymphoma	Phase I
			Combination*	Chronic lymphocytic leukaemia	Phase III
				B cell non-Hodgkin lymphoma	Phase I/II
				Diffuse large B cell lymphoma	Phase I/II
				Follicular lymphoma	Phase II
				Non-Hodgkin lymphoma	Phase II
S-055746	None	BCL-2	Single agent	Haematological malignancies including myelodysplasia	Phase I
PNT-2258	None	BCL-2	Single agent	Diffuse large B cell lymphoma	Phase II
				Follicular lymphoma	Phase II
				Non-Hodgkin lymphoma	Phase II

Data compiled from the Global Data database: http://healthcare.globaldata.com/ (accessed July 2015). *Combination with standard of care therapies.

Delbridge Nat Rev Cancer 2013

IAP targeted chemotherapeutics

Table 1. Clinical trials with Smac mimetics

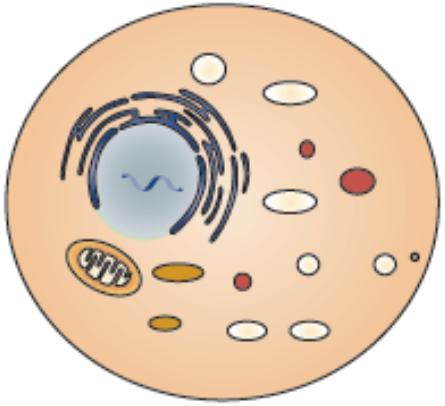
Compound	Combination	Cancer type	Status	Phase I/II
LCL-161	None	Solid tumors	Completed	Phase I
LCL-161	None	Leukemia	Recruiting	Phase II
LCL-161	Paclitaxel	Solid tumors	Completed	Phase I
LCL-161	Paclitaxel	Solid tumors	Recruiting	Phase I
LCL-161	Paclitaxel	Breast cancer	Completed	Phase II
LCL-161	Gemcitabine	Pancreatic cancer	Recruiting	Phase I
LCL-161	Cyclophosphamide	Multiple myeloma	Recruiting	Phase II
GDC-0152	None	Solid cancers	Completed	Phase I
CUCD-427	None	Lymphoma	Recruiting	Phase I
Birinapant	None	Solid tumors	Completed	Phase I/II
Birinapant	None	Solid tumors, lymphoma	Completed	Phase I
Birinapant	None	AML	Completed	Phase I/II
Birinapant	None	Ovarian, peritoneal and fallopian tube cancer	Completed	Phase II
Birinapant	Gemcitabine	Solid tumors	Terminated	Phase I
Birinapant	5-Aza	MDS	Active, not recruiting	Phase I/II
Birinapant	5-Aza	MDS, CMML	Recruiting	Phase II
Birinapant	Conatumumab	Ovarian, peritoneal and fallopian tube cancer	Recruiting	Phase I
AT-406	Daunorubicin, cytarabine	AML	Terminated	Phase I
Debio1143	None	Solid tumors, lymphoma	Completed	Phase I
Debio1143	Paclitaxel, carboplatin	Solid tumors	Recruiting	Phase I
Debio1143	Cisplatin, radiotherapy	Head and neck carcinoma	Recruiting	Phase I/II
HGS1029	None	Solid tumors	Completed	Phase I
HGS1029	None	Lymphoid malignancies	Terminated	Phase I

Abbreviations: 5-Aza, 5-Azacitidine; AML; acute myelogenous leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome.

Fulda Clin Cancer Res 2015

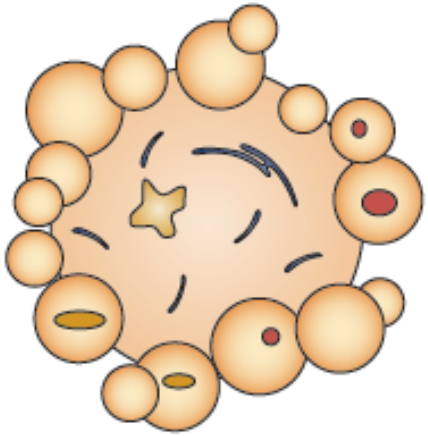
diversi tipi di morte cellulare

autofagia



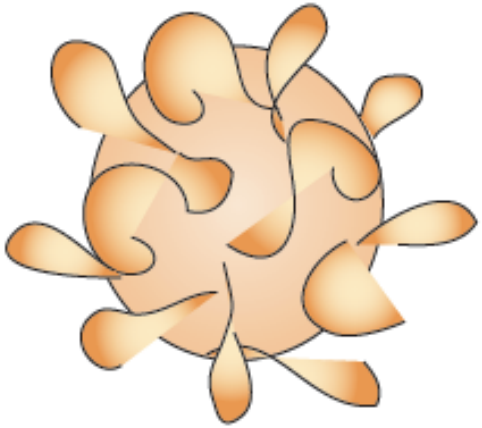
formazione
di autofagosomi

apoptosi



vescicolazione

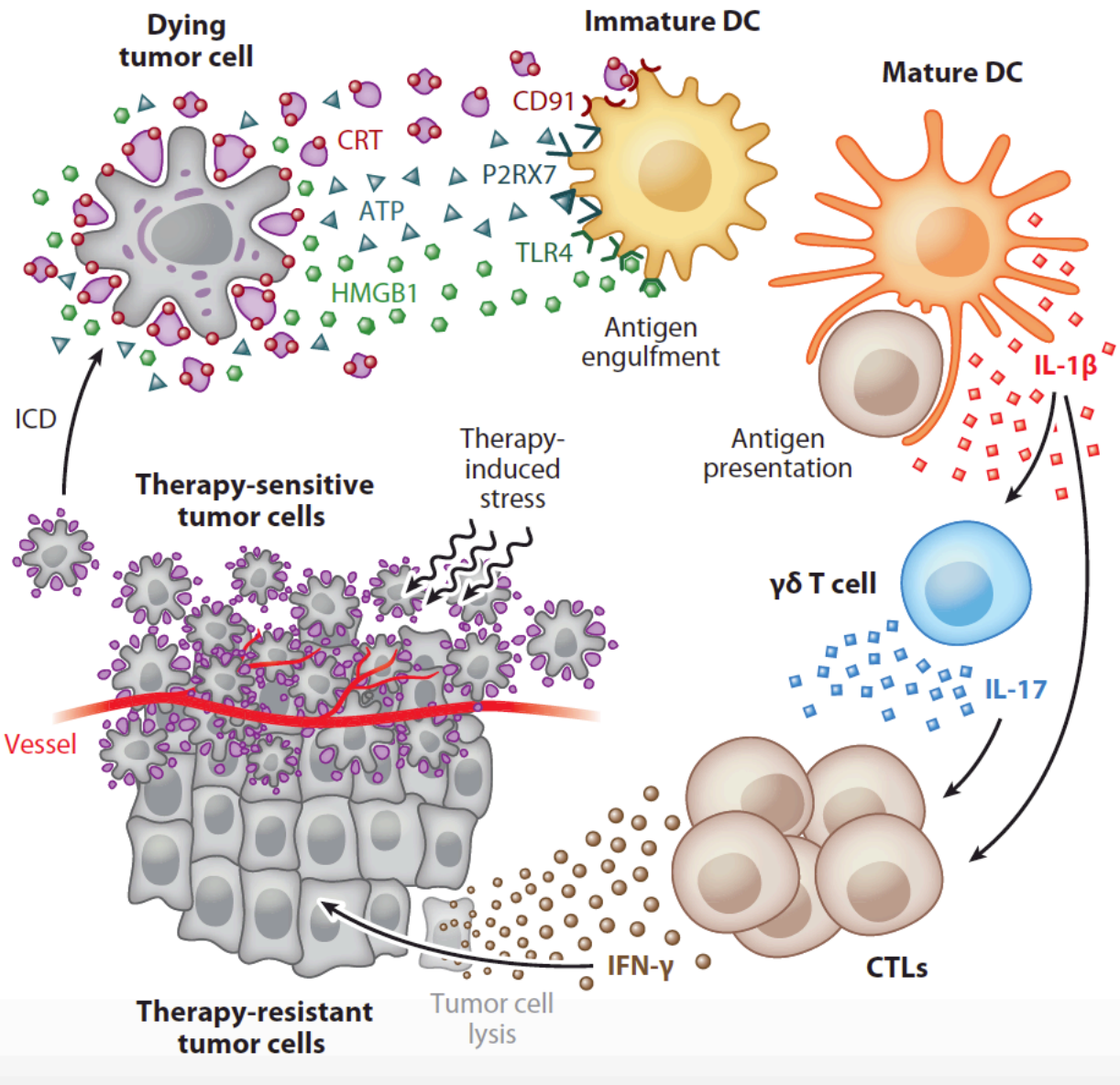
necrosi



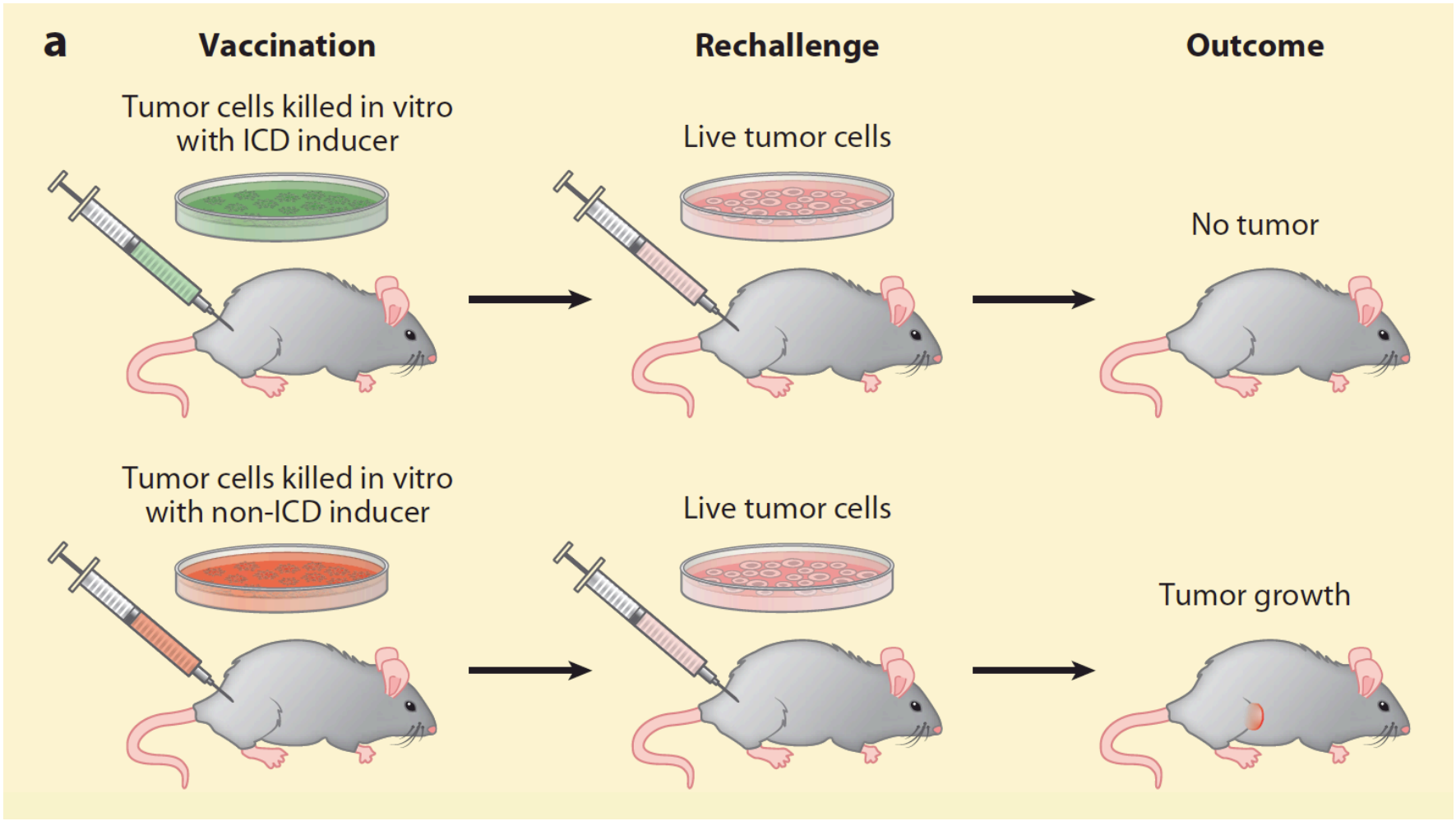
lisi

Induzione di morte cellulare immunogenica e non immunogenica:

Calreticulin, HSPs, Release of DAMP (damage-associated molecular patterns: ATP, HMGB1…)



Induzione di morte cellulare immunogenica e non immunogenica: implicazioni terapeutiche



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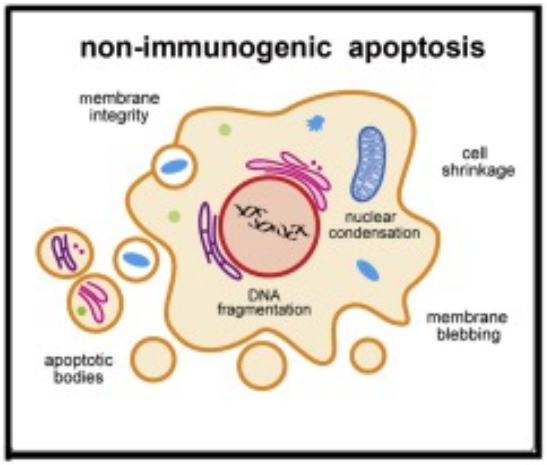
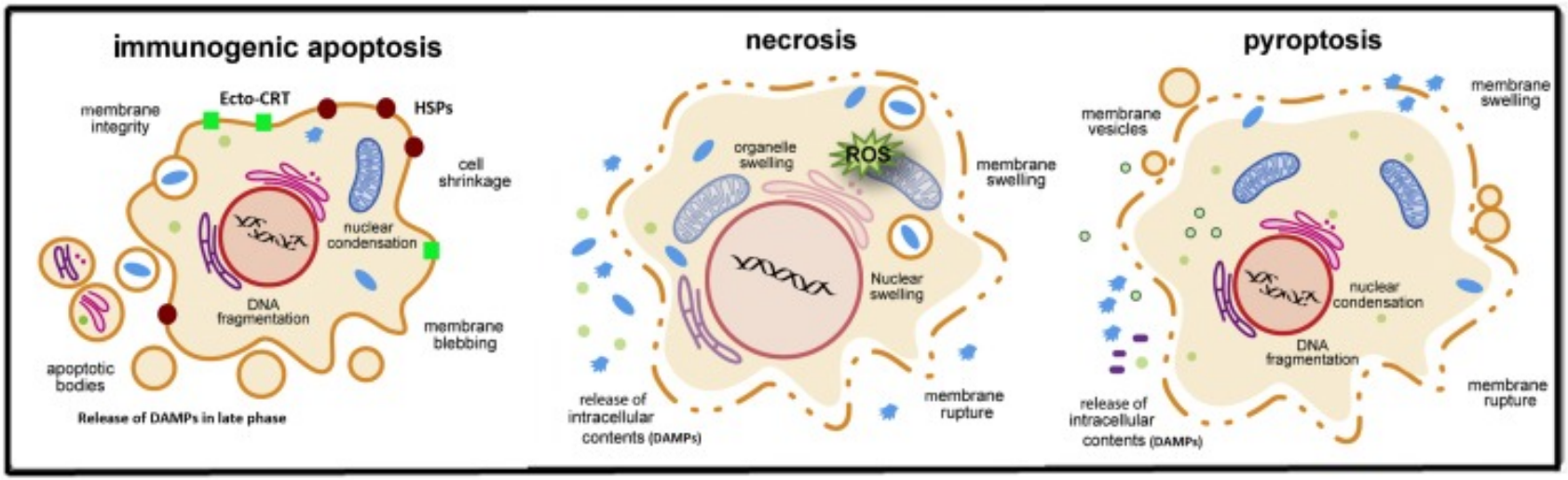


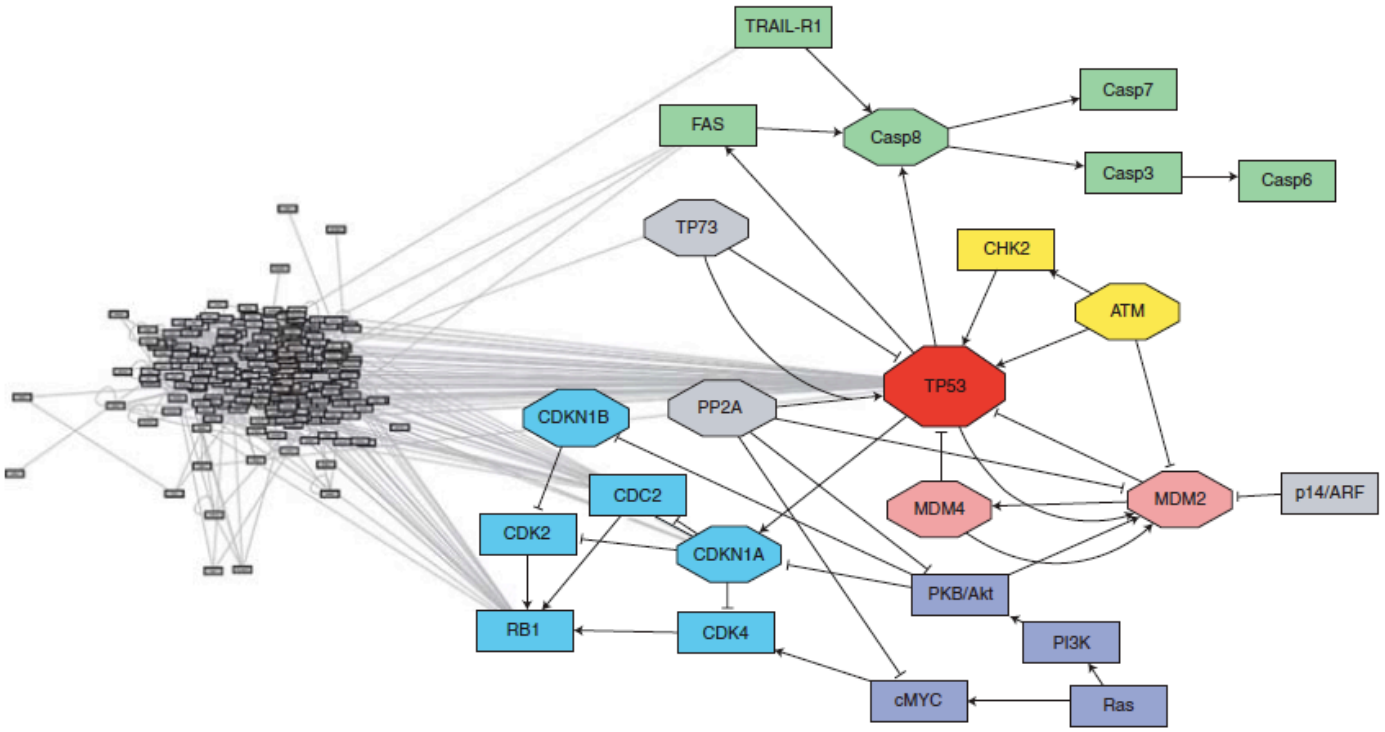
Non-immunogenic cell death mode

Immunogenic cell death modes



Polimorfismi nella pathway di p53: implicazioni per il rischio tumorale

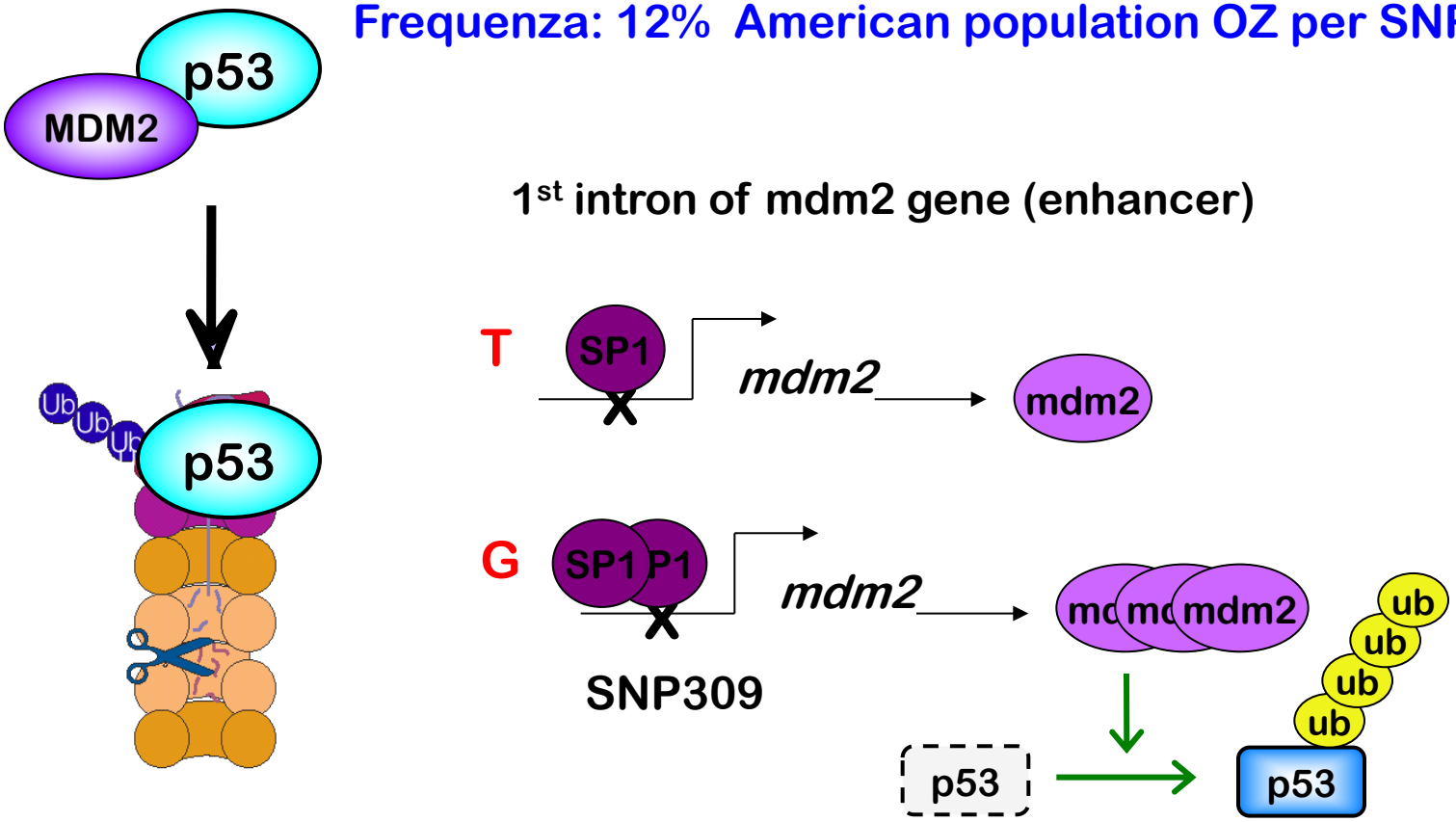
the p53 pathway harbors single-nucleotide polymorphisms (SNPs)
that affect p53 signaling
resulting in differences in cancer risk and clinical outcome in humans



more than 50,000 SNPs in the NCBI SNP repository in genes implicated in mediating and regulating the p53 response *(Vazquez et al. 2008).*

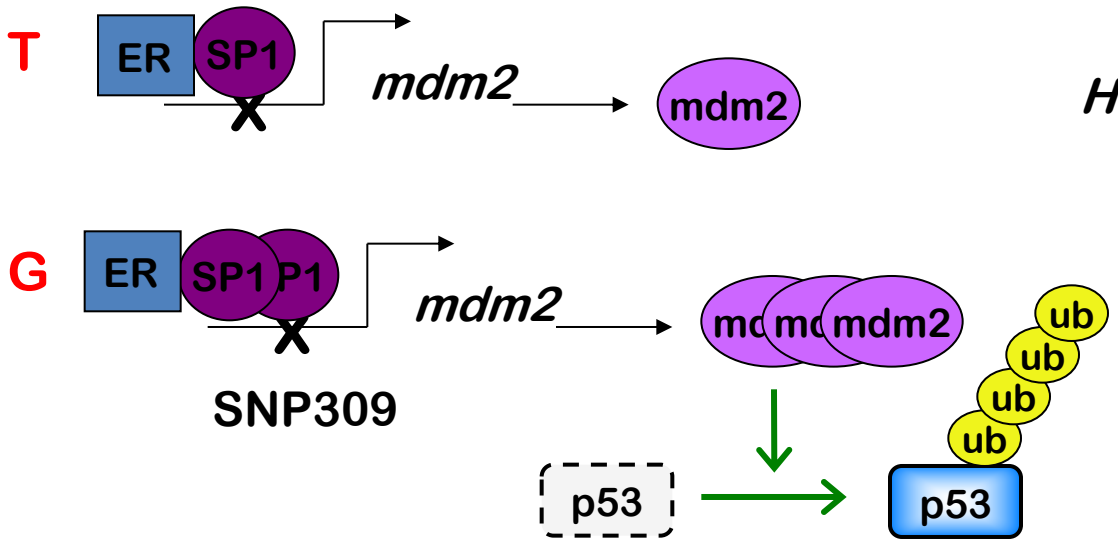
Mdm2 SNP309

Frequenza: 12% American population OZ per SNP309



Cellule con genotipo G/G esprimono quantità 4-volte maggiore di Mdm2: La risposta di p53 è attenuata (in vitro e in modelli sperimentali di tumorigenesi in vivo)

Gli estrogeni promuovono la trascrizione di HDM2



Hu et al. 2007

I livelli di Mdm2 aumentano in cellule responsive agli estrogeni

Aumento del rischio di tumori responsivi agli estrogeni, es. ER+ breast cancer (età media 45 anzichè 57)

~65% dei breast tumours sono ER +

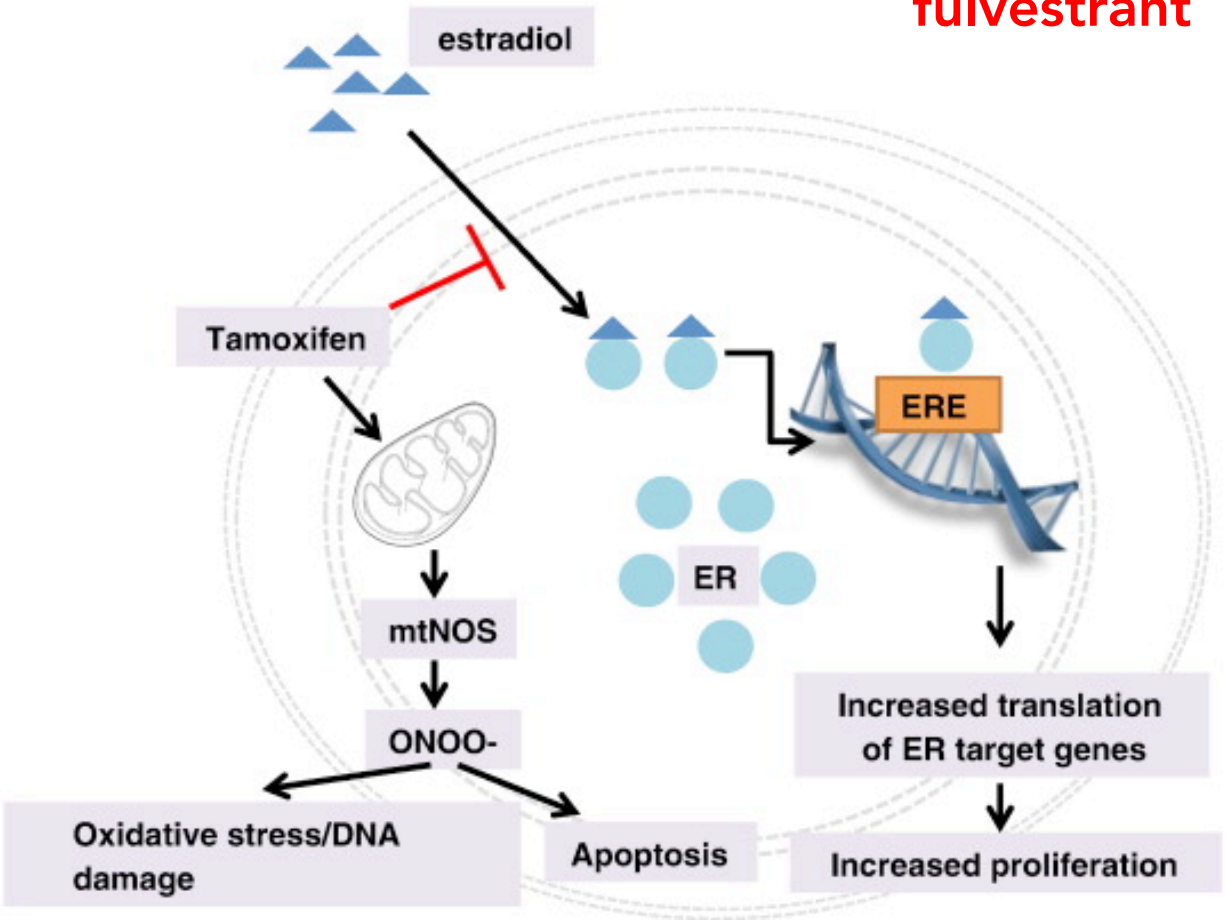
⇨Mostrano risposta proliferativa agli estrogeni (ovaries)

⇨ beneficiano di terapia anti-estrogeni

Tamoxifen (anti-ER therapy)

Aromatase inhibitors

fulvestrant

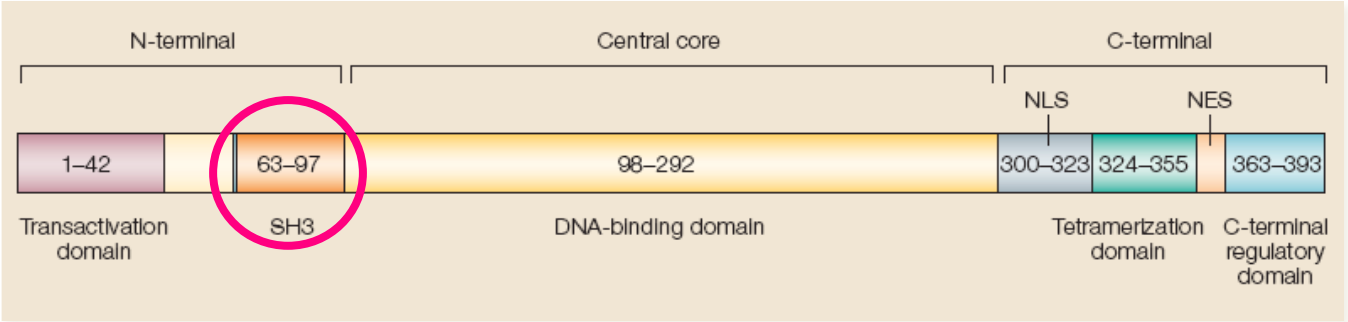


Implicazioni cliniche

La terapia ormonale sostitutiva in donne con genotipo G/G,
può aumentare significativamente il rischio di cancro.

Al contrario tali pazienti beneficerebbero di terapie anti-estrogeniche

Il polimorfismo del codone 72



p53-Arg72 :

•Comune: frequenza nella popolaz caucasica Pro/Pro 5%; Arg/Pro 50%; Arg/Arg 40%

• Arg72 ha maggiore attività proapoptotica di Pro72

maggiore attività di soppressione tumorale e risposta a terapie convenzionali

Thomas et al., 1999; Bonafe et al., 2002; Dumont et al., 2003; Sullivan et al., 2004; Pim et al., 2004; Bergamaschi et al., 2006.

NB: l'effetto su MUTANT p53 è opposto

Cells bearing mutp53 Pro72 form undergo more apoptosis compared to isogenic Arg72

Marin et al., 2000; Bergamaschi et al., 2003; Vikhanskaya et al. 2005