

SLA e mitocondri

sporadica

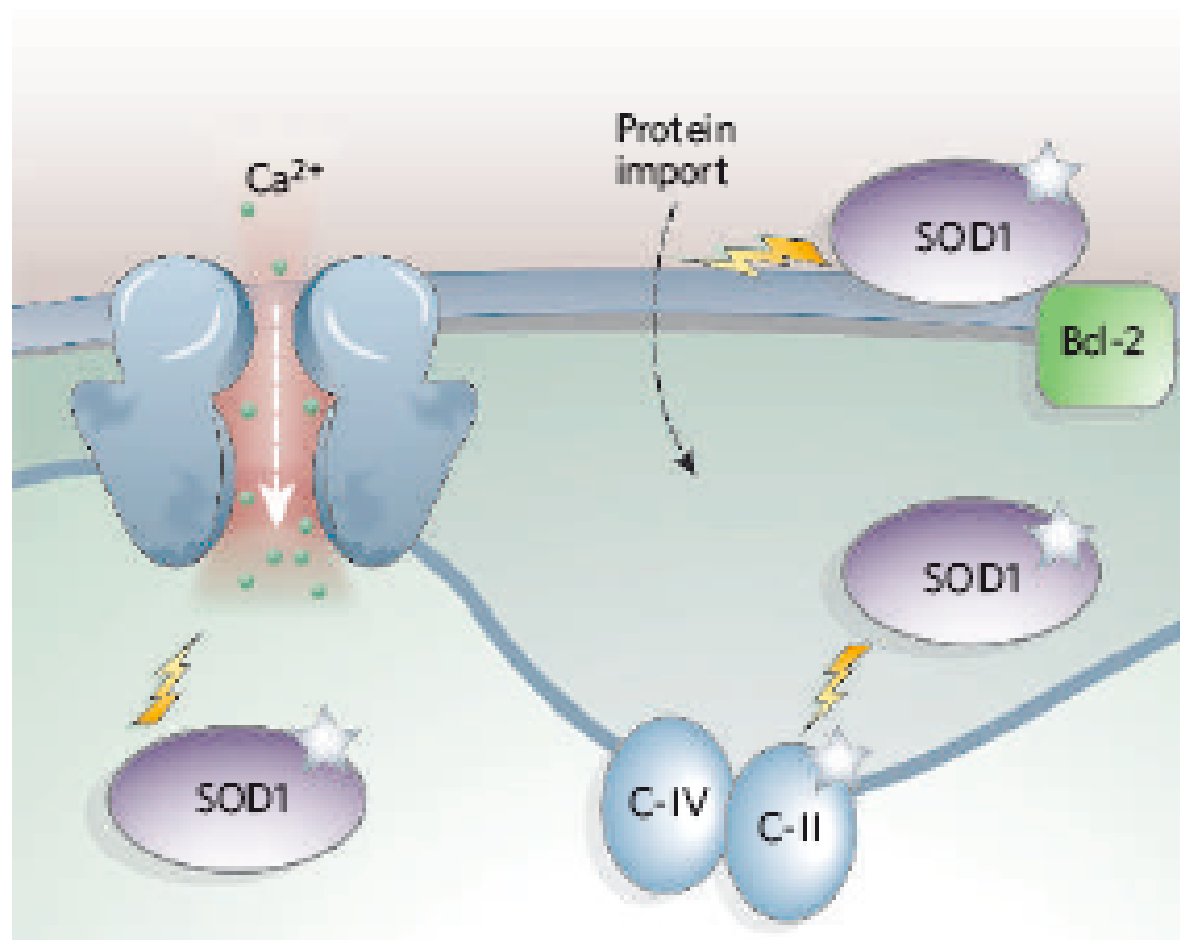
↓ attività del Complesso II e IV
↑ stress ossidativo

Amyotrophic lateral sclerosis

genetica

SOD1

citosolica
e
mitocondriale



Huntington e mitocondri

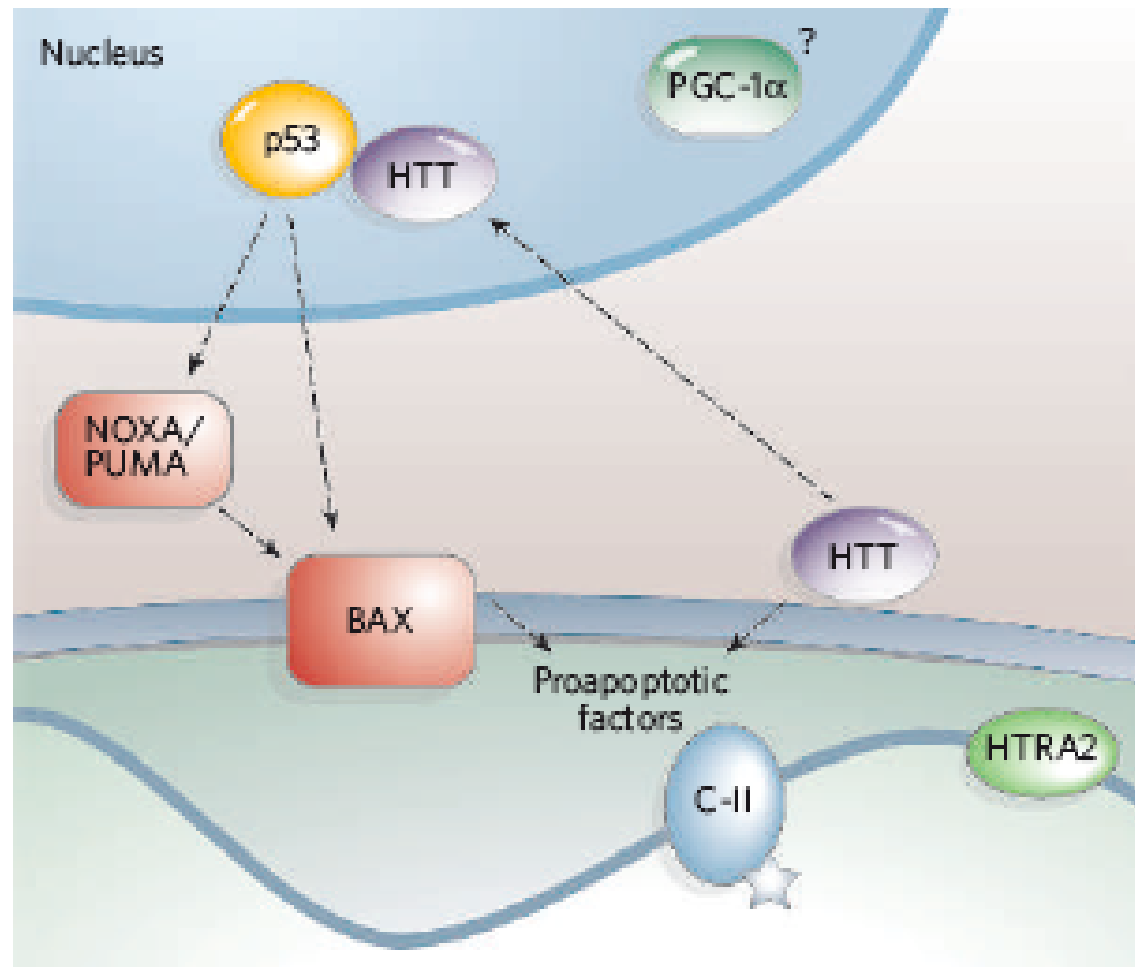
↓ attività del Complesso II e III

acido 3-nitropropionico (C2) induce HD

genetica

Htt

nucleare
e
mitocondriale



Altre neurodegenerazioni e mitocondri

Table 2 | Mitochondrial involvement in less common neurodegenerative diseases

Disease	Clinical features	Protein	Function
Friedreich's ataxia	Ataxia and neuropathy due to degeneration of spinocerebellar tracts and dorsal-root ganglia; diabetes; cardiomyopathy Autosomal recessive	Frataxin	A mitochondrial iron chaperone that promotes the biogenesis of enzymes with Fe-S clusters and detoxifies excess iron. Frataxin deficiency causes iron accumulation and impairs the activity of Fe-S cluster-containing enzymes (complexes I and II, and aconitase). It may also perturb manganese balance and impair MnSOD activity
Hereditary spastic paraplegia (HSP)	Slowly progressive weakness and spasticity of the legs Autosomal recessive	SPG7*	An inner mitochondrial membrane m-AAA metalloprotease. It functions as a chaperone and is involved in the assembly of respiratory-chain complexes. SPG7 deficiency causes recessive HSP with mitochondrial myopathy
	Autosomal dominant	SPG13 [†]	A mitochondrial protein chaperone
Neurodegeneration with brain iron accumulation (NBIA)	Progressive dementia, rigidity, involuntary movements, spasticity and retinal degeneration accompanied by iron deposition in globus pallidus and substantia nigra Autosomal recessive, paediatric onset	PANK2	PANK2 is localized to mitochondria and catalyses the first step in coenzyme A synthesis. PANK2 deficiency is the most common cause of NBIA, accounting for ~50% of cases
Optic atrophy type 1	Autosomal dominant optic neuropathy causing progressive visual loss	OPA1	OPA1 is a dynamin-related GTPase localized to mitochondria. It organizes the mitochondrial inner membrane and is necessary for maintaining cristae integrity. SiRNA knockdown of OPA1 causes fragmentation of the mitochondrial network, loss of mitochondrial membrane potential, disorganization of cristae, release of cytochrome c and activation of caspases

*Also known as paraplegin. [†]Also known as heat-shock protein 60. m-AAA, mitochondrial ATPases associated with diverse cellular activities; PANK2, pantothenate kinase 2; SPG, spastic paraplegia gene.

mitocondri e morte cellulare

NECROSI :

- ✓ le cellule non eseguono un programma preesistente
- ✓ indotta da privazione energetica, stress ossidativo, stress ionico
- ✓ “veloce” (insulti acuti)
- ✓ non rilevante per lo sviluppo e il turn-over dei tessuti

APOPTOSI:

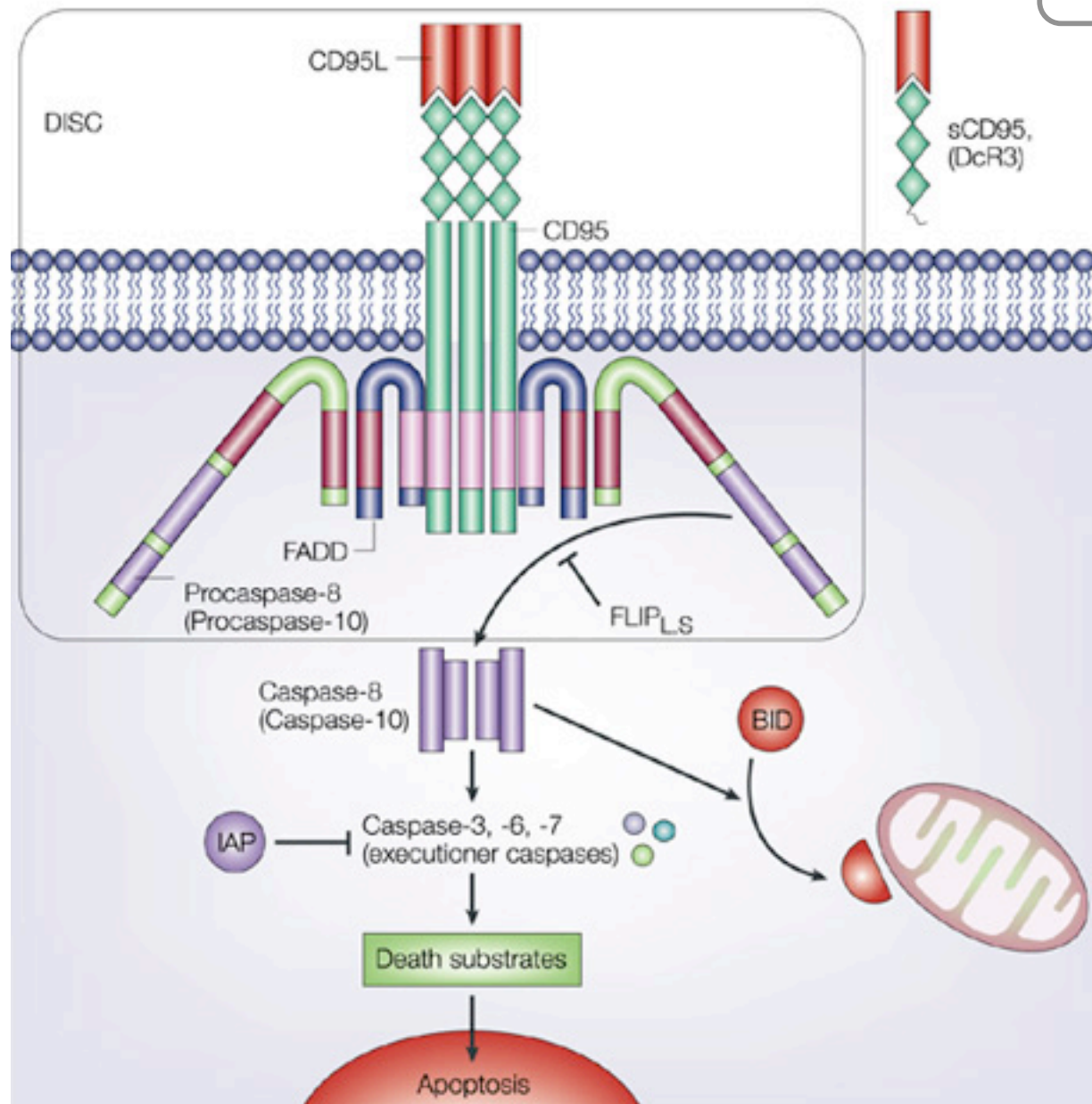
- ✓ le cellule eseguono un programma preesistente
- ✓ produzione e coinvolgimento di proteine esecutrici
- ✓ mitocondriale (intrinseca) e recettoriale (estrinseca)
- ✓ rilevante per lo sviluppo e il turn-over dei tessuti
- ✓ “lenta” (insulti cronici)

AUTOFAGIA

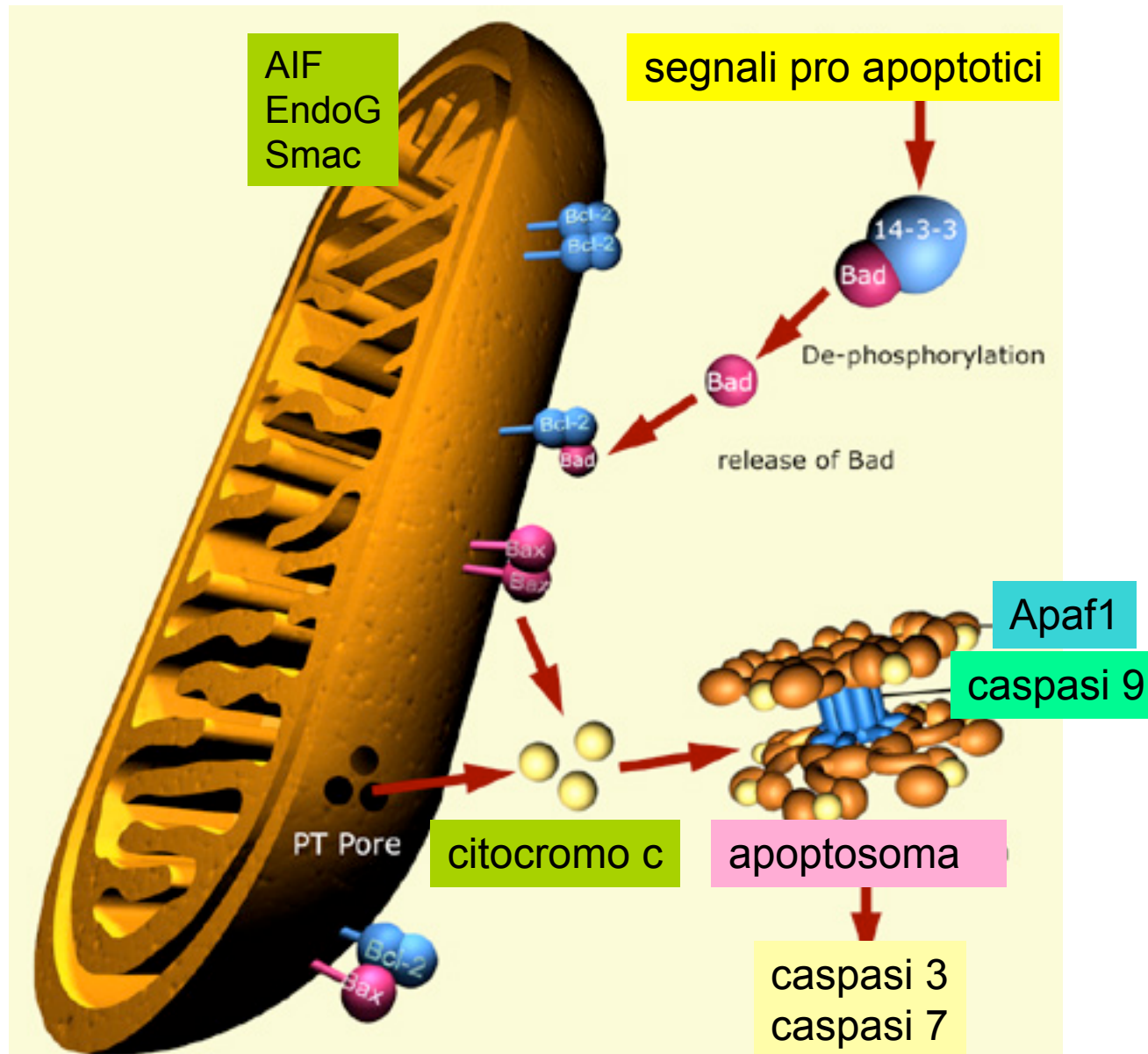
Apoptosi recettoriale

Stimoli
death ligands

Esecuzione
Formazione del DISC
casp8 iniziatrice
casp3,6,7 esecutrici



Apoptosi mitocondriale



Stimoli

Danno al DNA
ROS
Fas
?

Caspasi dipendente

casp9 iniziatrice

casp7

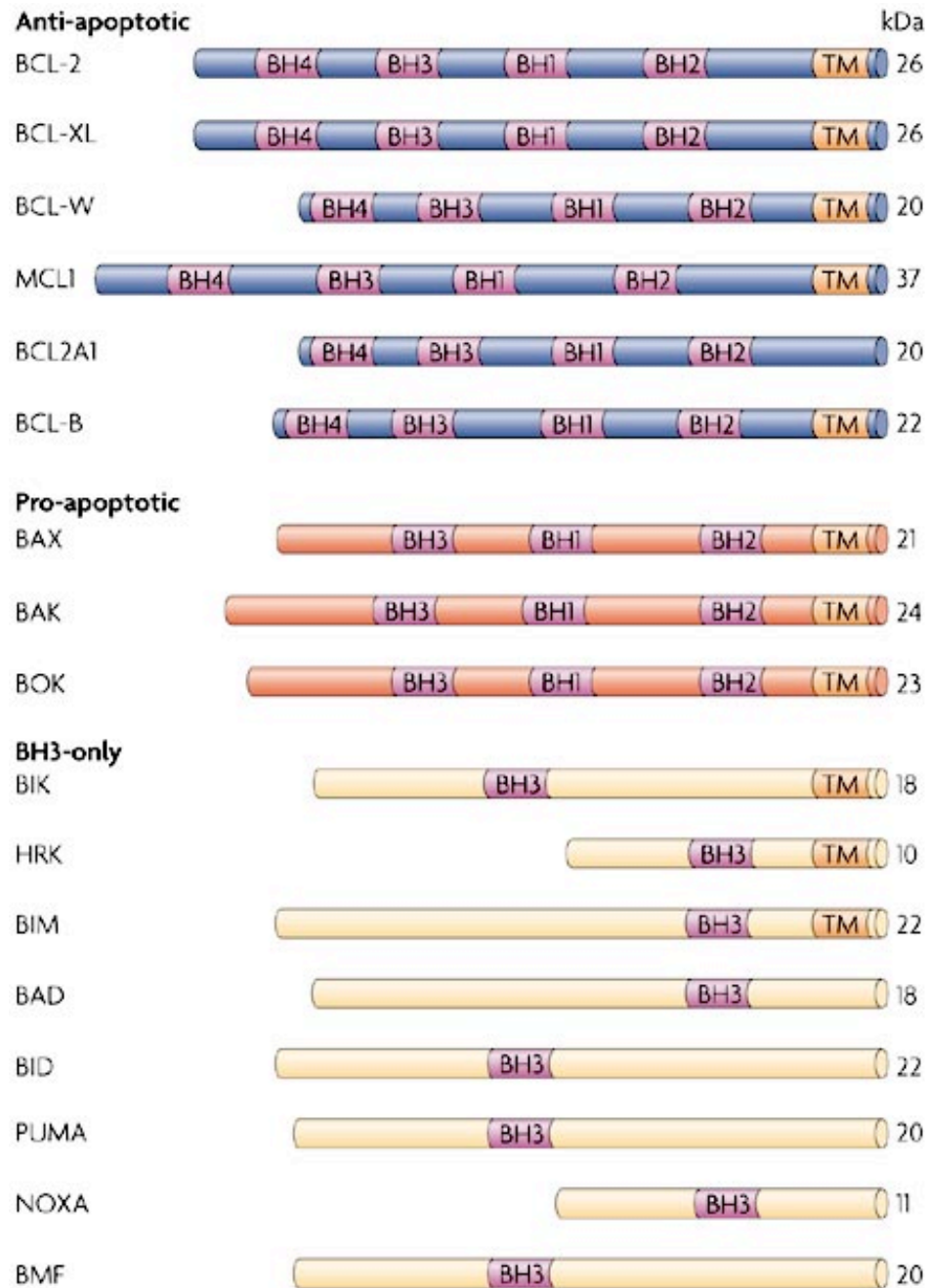
casp3 esecutrici

Caspasi indipendente

AIF

EndoG

Smac/Diablo

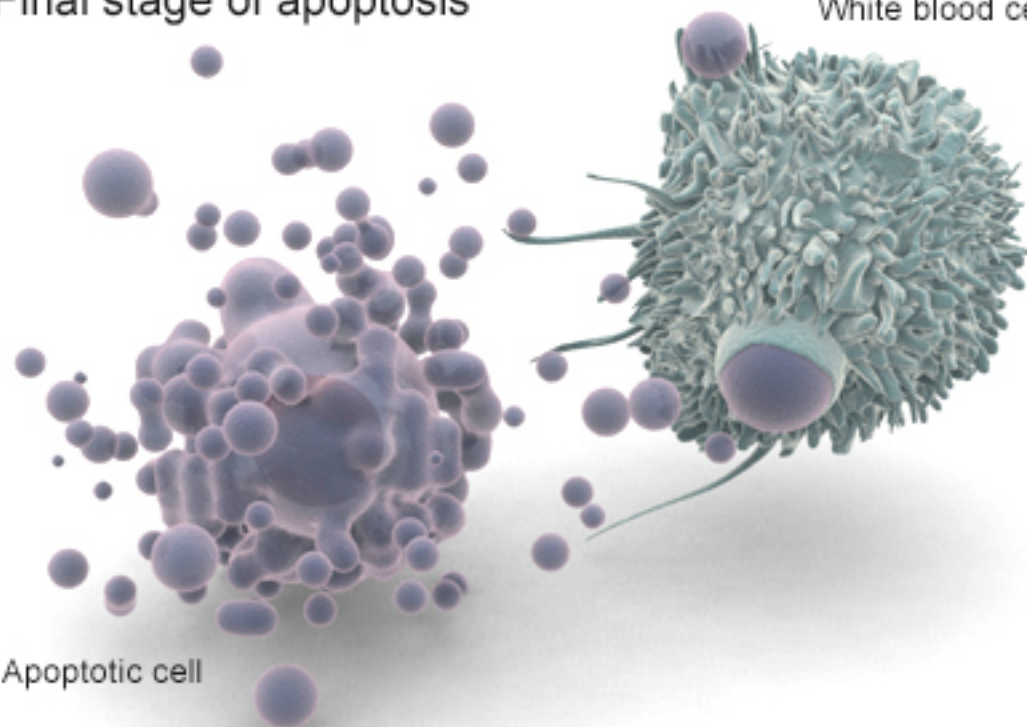


Famiglia **bcl2**
di geni

pro-apoptotici
anti-apoptotici

Final stage of apoptosis

White blood cell

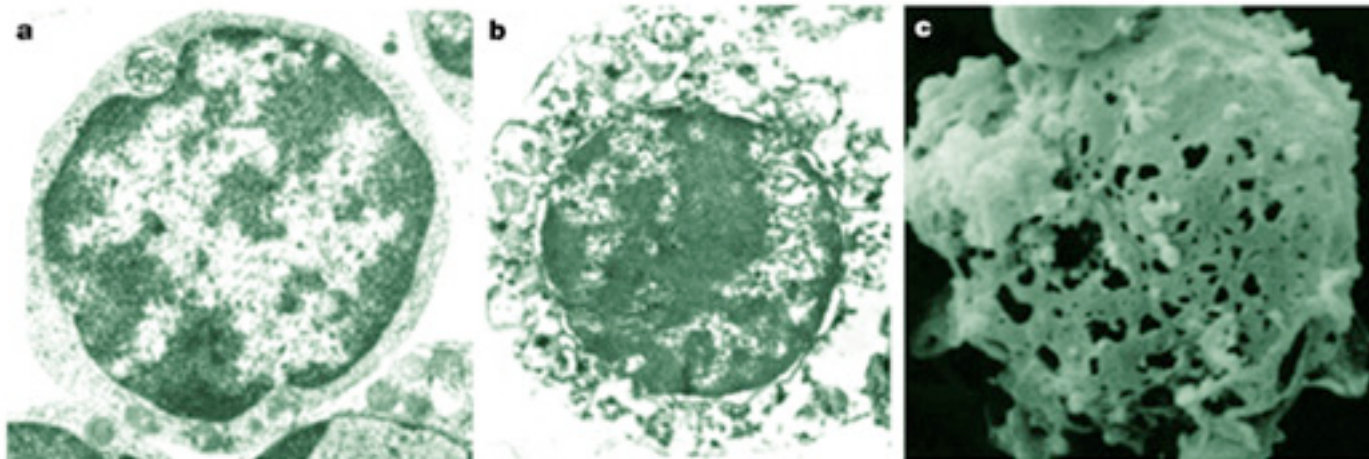


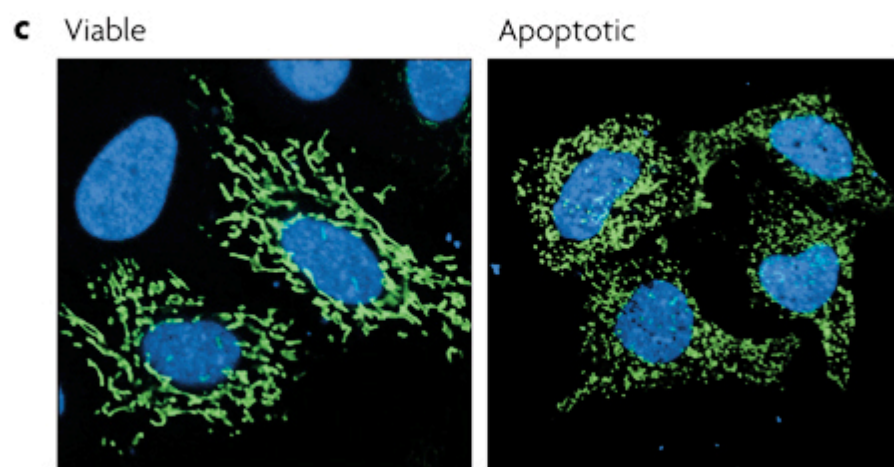
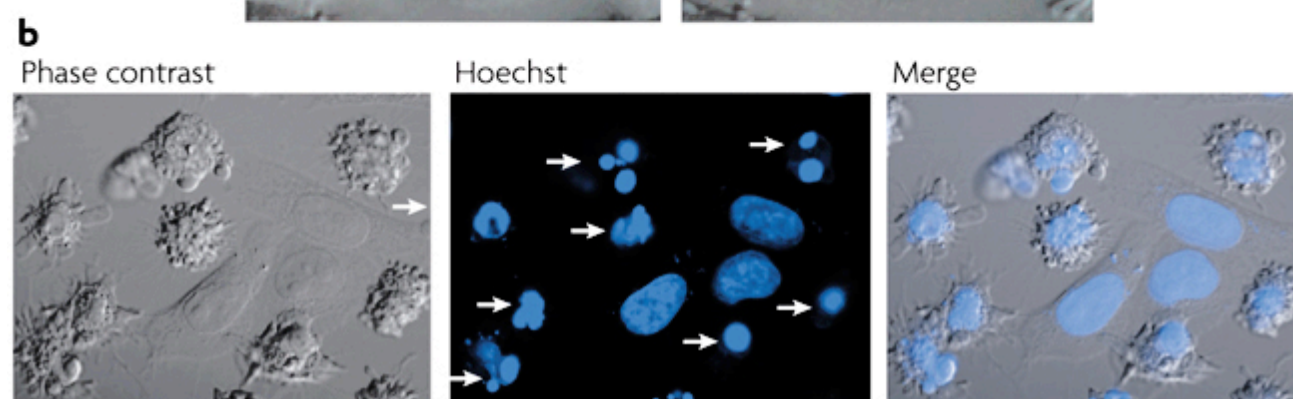
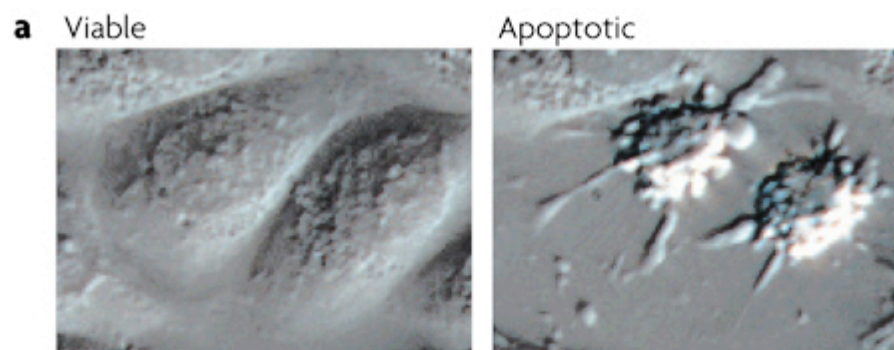
apoptosi

Apoptotic cell

necrosi

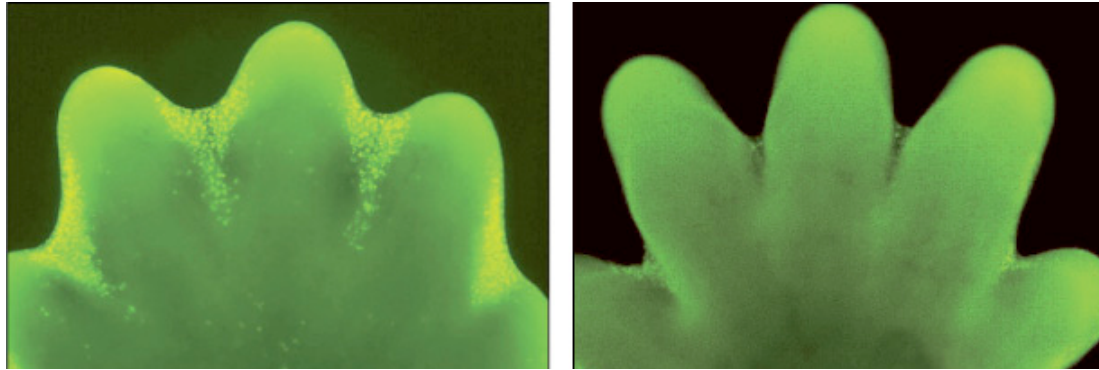
U.S. National Library of Medicine



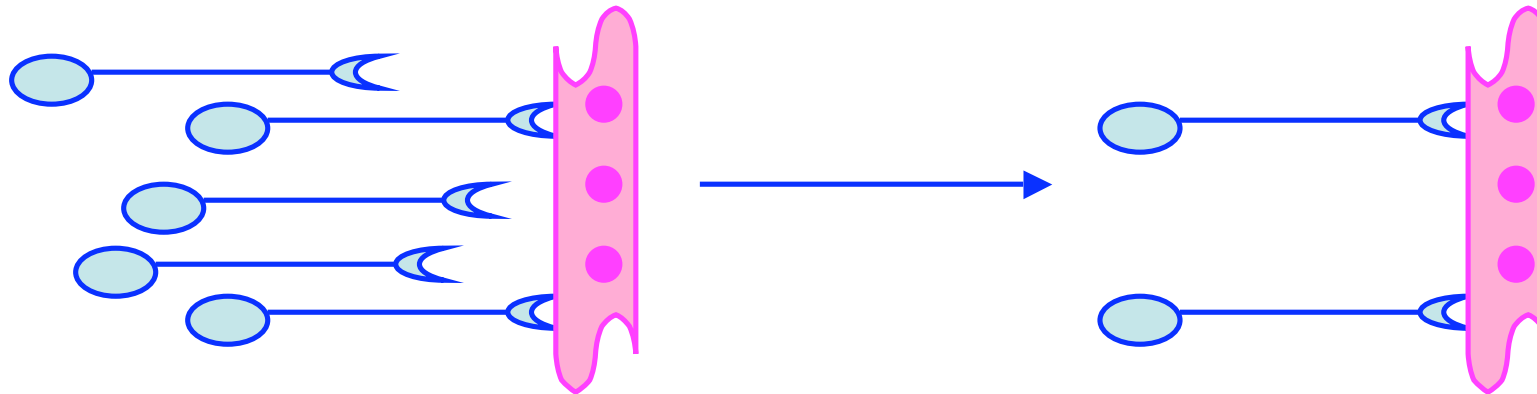


Apoptosi e embriogenesi

Morfogenesi: elimina cellule in eccesso



Selezione: elimina cellule non funzionanti



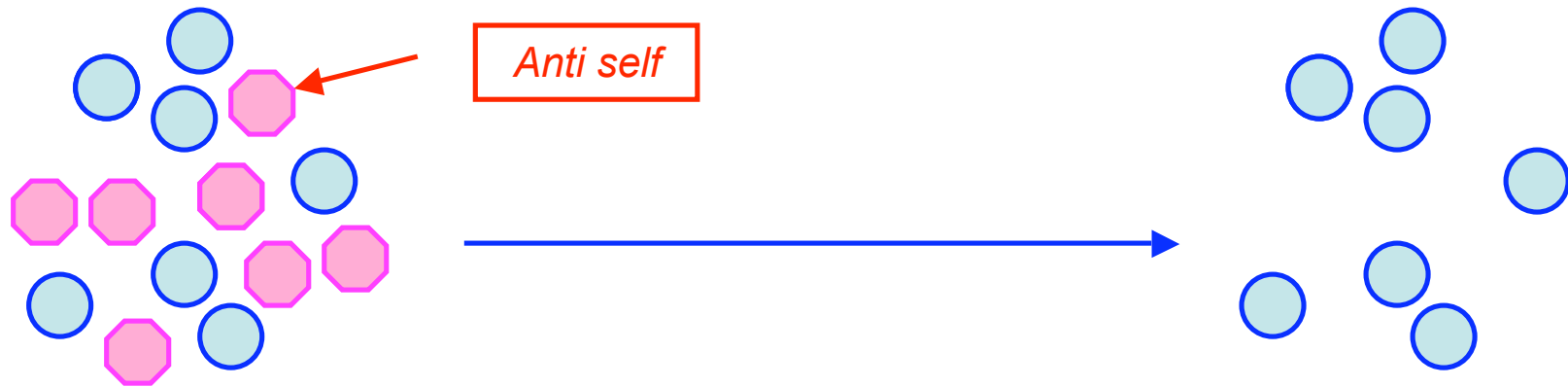
Topi knock-out per le caspasi mostrano fenotipi neuronali

Table 1 Neuronal phenotypes of caspase-knockout mice

Caspase	Development	Neuronal apoptotic phenotype	References
Caspase-1	Normal	Resistant to ischaemic brain injury and a decrease in incidence and severity of experimental autoimmune encephalomyelitis	98
Caspase-2	Normal	Hippocampal neurons from caspase-2-null mice are resistant to amyloid- β (1–42) toxicity	66
Caspase-3	Perinataly lethal (depend on genetic background)	Lack of apoptosis in neuroepithelial progenitor cells during development	22
Caspase-9	Embryonic lethal (a small percentage of caspase-9-knockout can survive to adult)	Lack of apoptosis in neuroepithelial progenitor cells during development	23,99
Caspase-11	Normal	Resistant to apoptosis induced by ischaemic brain injury	20
Caspase-12	Normal	Cortical neurons are resistant to amyloid- β toxicity	21

Apoptosi ed embriogenesi

Immunità: elimina cellule pericolose

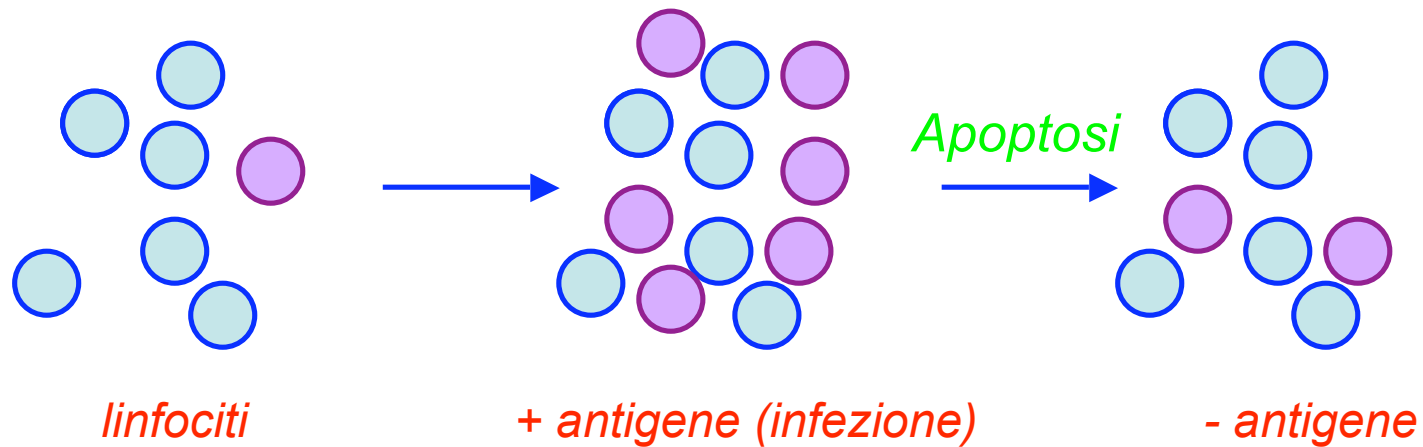


Organogenesi: elimina cellule in eccesso



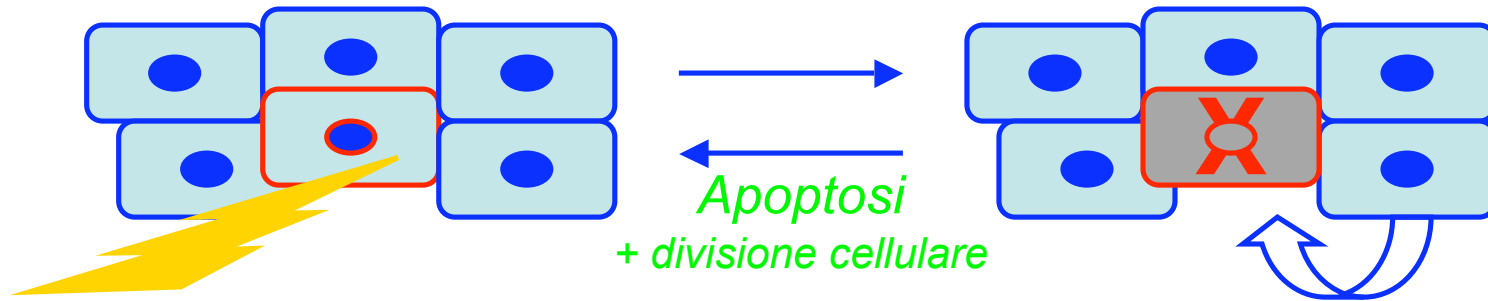
Apoptosi nell'adulto

Rimodellamento dei tessuti: elimina cellule non più utili



Apoptosi nell'adulto

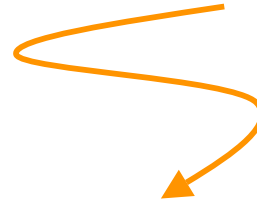
Mantiene dimensione e funzioni dei tessuti:



Cellule perse per apoptosi sono rimpiazzate attraverso la divisione cellulare.....

Apoptosi e neurodegenerazioni

- ✓ I neuroni sono post-mitotici
 - non possono sostituire se stessi
 - il rimpiazzo dalle cellule staminali neuronali è insufficiente
- ✓ Perdita delle connessioni, di fattori di crescita, danni causano disfunzioni neuronali che si manifestano come
 - perdita delle sinapsi **sinaptosi** (reversibile)
 - perdita del corpo cellulare **apoptosi** (irreversibile)



NEURODEGENERAZIONE

Apoptosi e neurodegenerazioni

Nelle malattie croniche l'apoptosi è un processo lento

→ poche cellule apoptotiche in un dato momento

✓ Criteri morfologici:

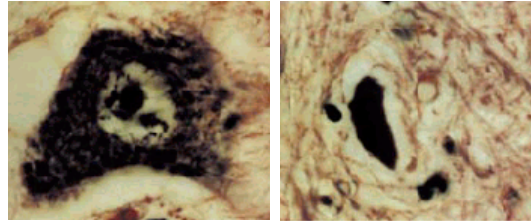
- morfologia dei nuclei
- morfologia delle cellule

✓ Criteri biochimici

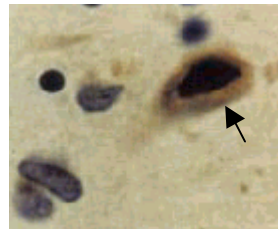
- DNA ladder
- attivazione di caspasi
- attivazione/disattivazione di fattori pro/antiapoptotici

Apoptosi e SLA

Morfologia



TUNEL



Inibitori apoptosi: XIAP



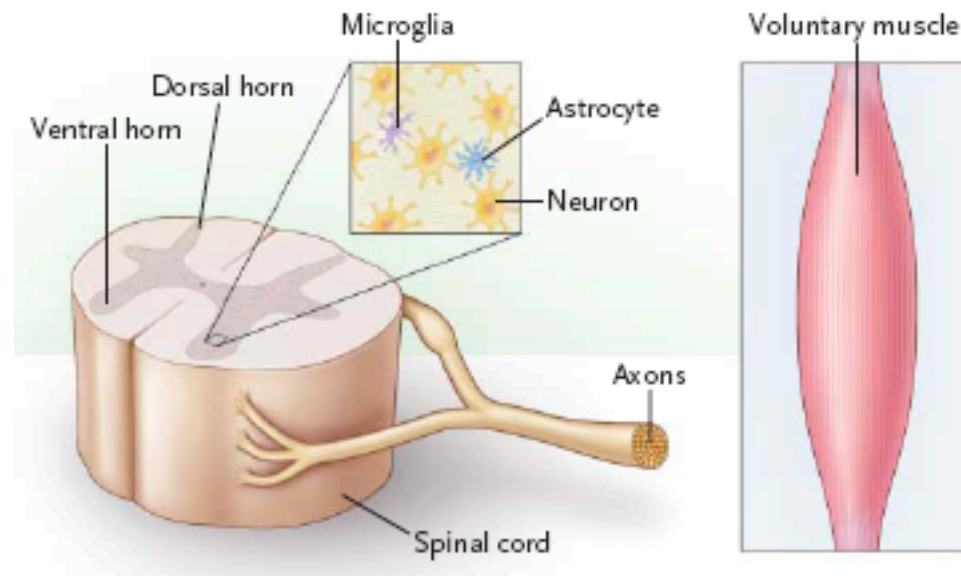
Famiglia di Bcl-2: Bcl-2
Bax



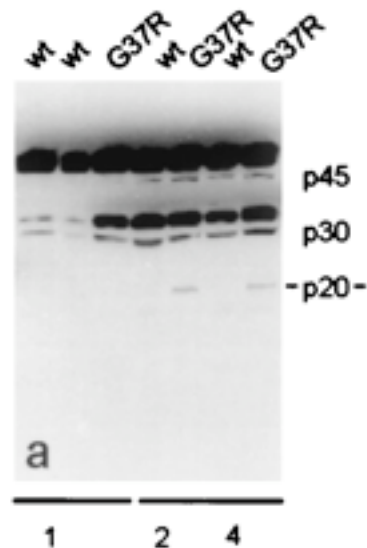
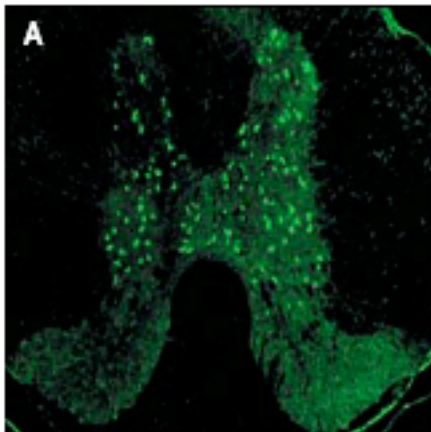
Attivazione caspasi:

caspase-1 ↑
caspase-3 ↑

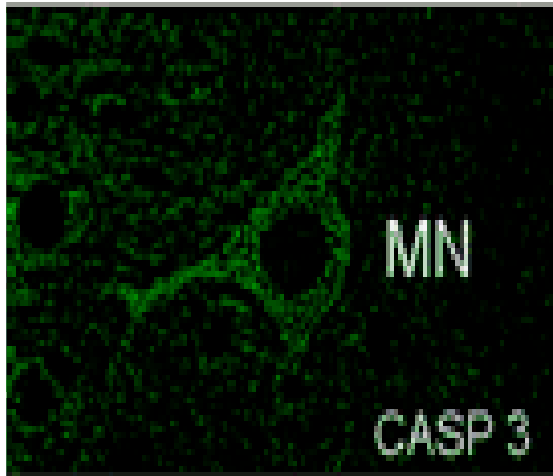
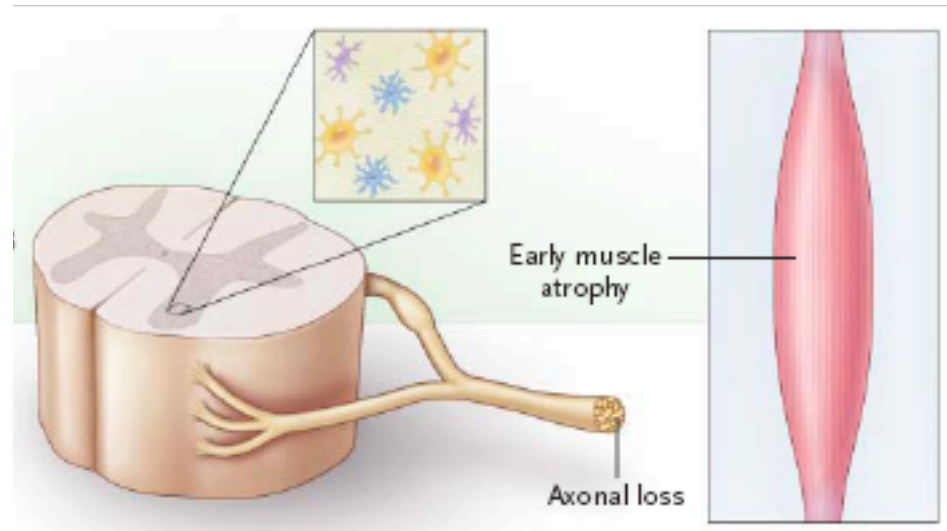
fase presintomatica



attivazione caspasi1

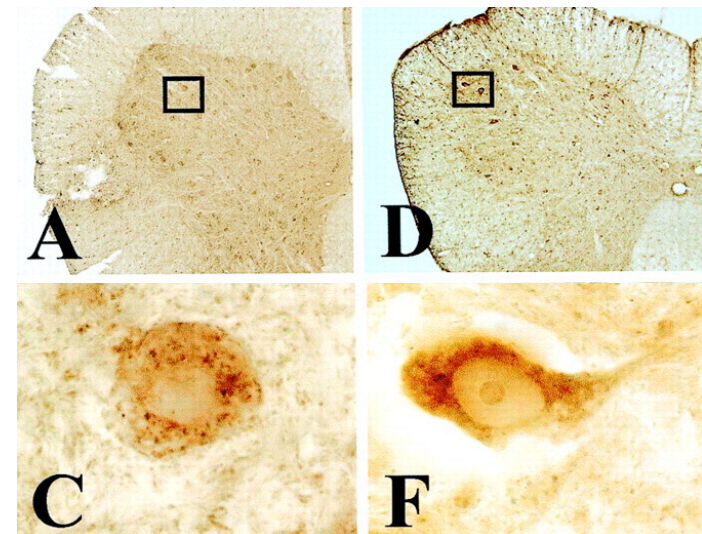


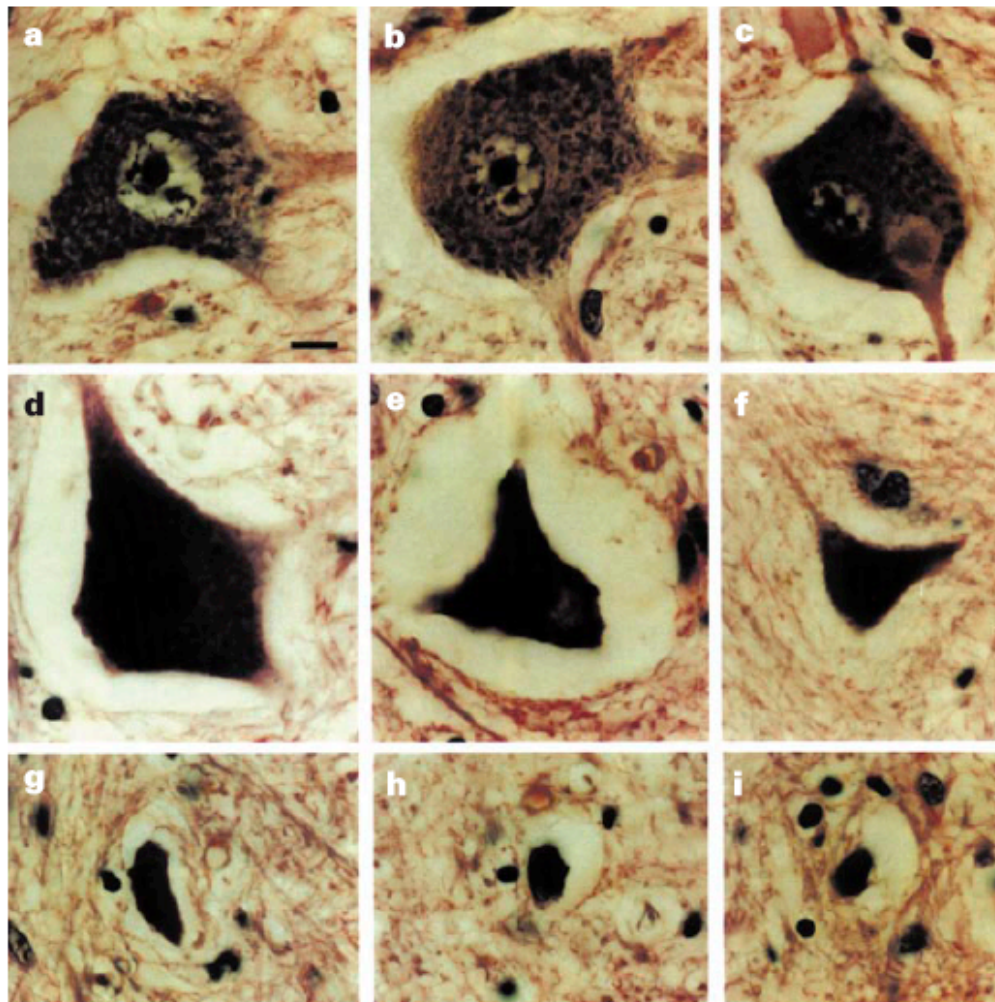
fase sintomatica (inizio)



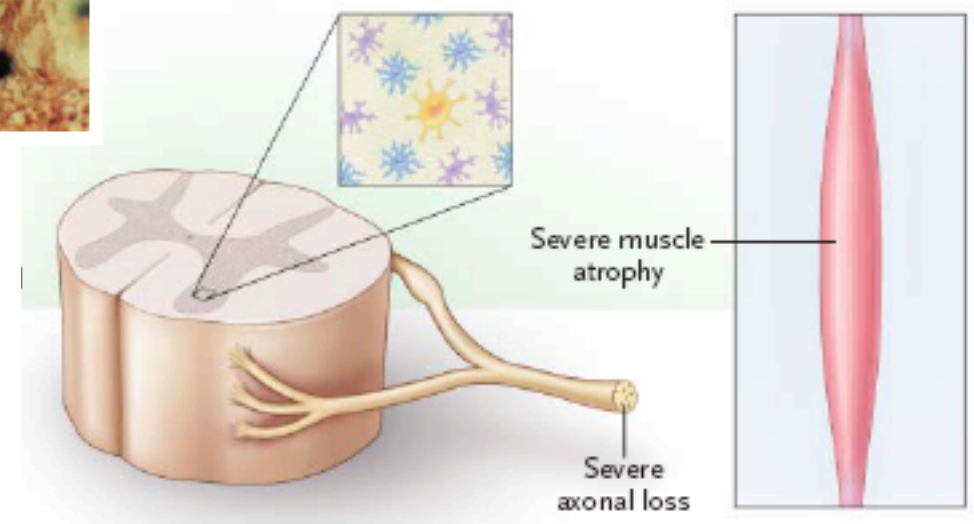
attivazione casp3

rilascio citocromo c





fase sintomatica (fine)

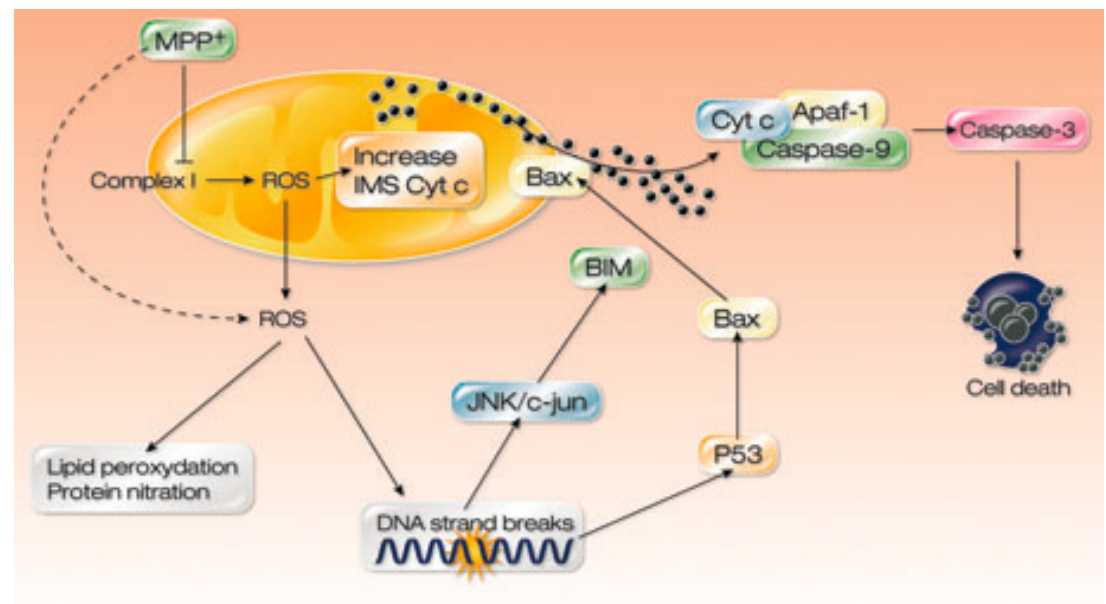


Apoptosi e Parkinson

Topi MPTP: rilascio cit c
attivazione casp3 casp9
attivazione Bax

Topi α -syn: attivazione casp3
TUNEL

Uomo: attivazione casp3 casp9
attivazione Bax



Apoptosi e Huntington

Http: proteina antiapoptotica
tagliata dalla casp3 e casp6

Topi mtHttp: rilascio cit c
R6/2 attivazione casp1 casp3 casp8 casp9
attivazione Bax

Uomo: rilascio cit c
casp3 casp8 casp9

Ca²⁺, mitocondri e neurodegenerazione

Gradiente [Ca²⁺] attraverso le membrane:

1mM extracellulare

50-100nM intracellulare

Le cellule utilizzano questo gradiente come meccanismo di segnalazione intracellulare

Nelle cellule nervose la segnalazione Ca²⁺-dipendente controlla:

crescita neuritica

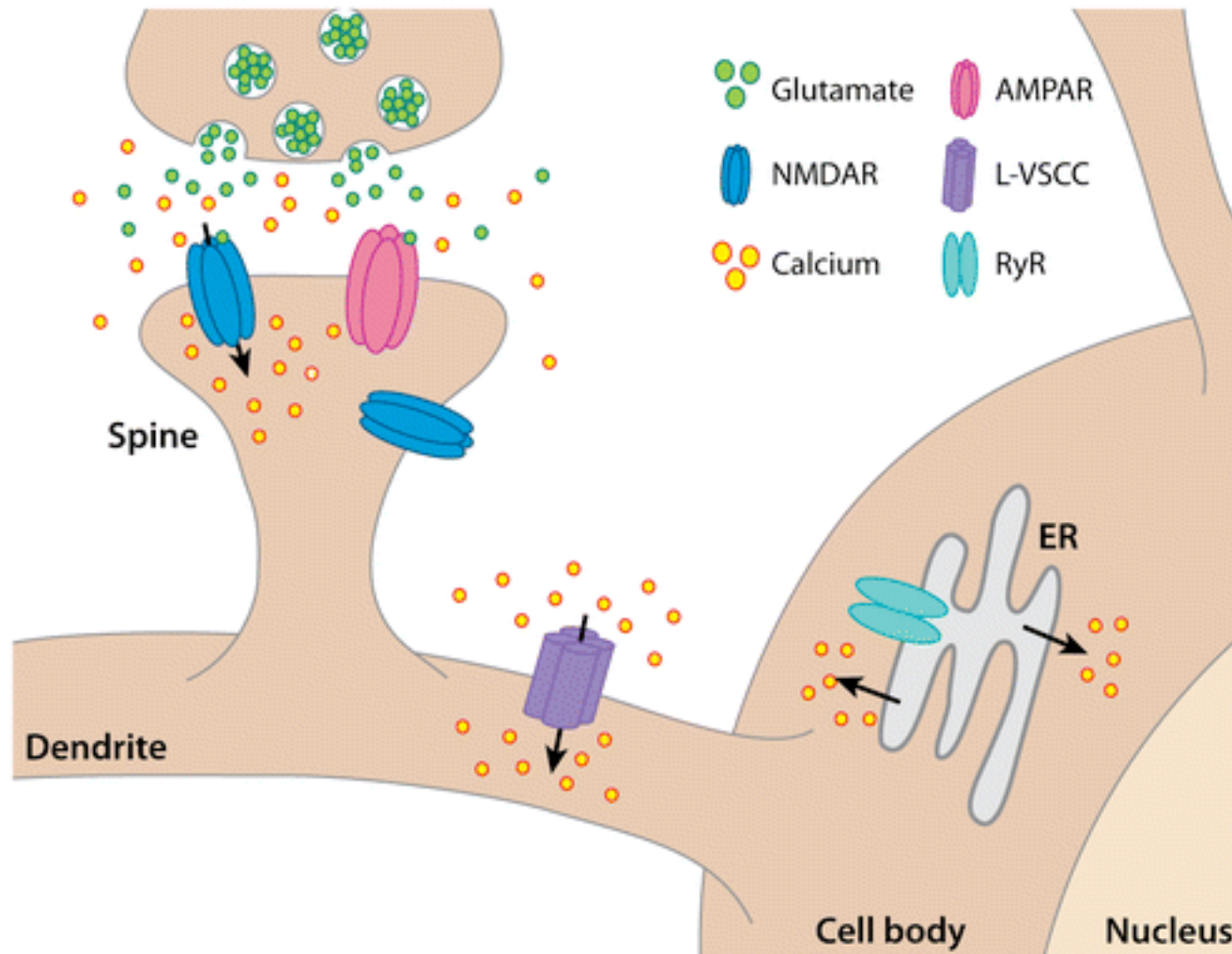
sinaptogenesi

trasmissione sinaptica

plasticità sinaptica

sopravvivenza cellulare

Ca²⁺, mitocondri e neurodegenerazione



Recettori del
glutammato

ionotropici

NMDA

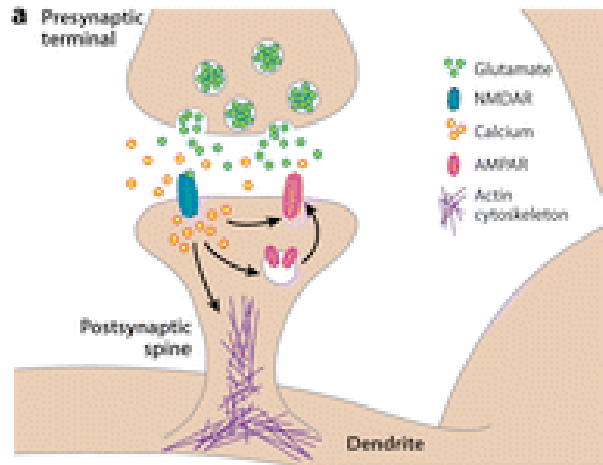
AMPA

Metabotropici

GluR

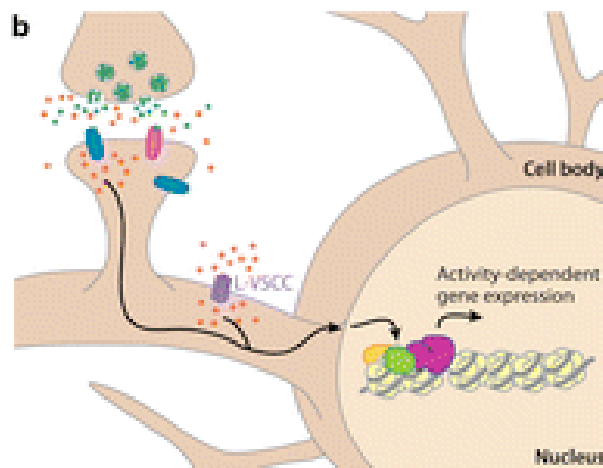
Canali

VSCC

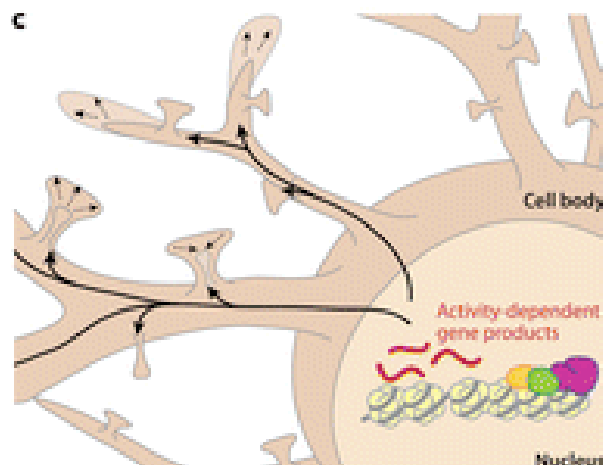


✓ Rilascio di glutammato
attivazione NMDA
(AMPA)

✓ Flusso di calcio attraverso
NMDA e VSCC



✓ Induzione espressione genica

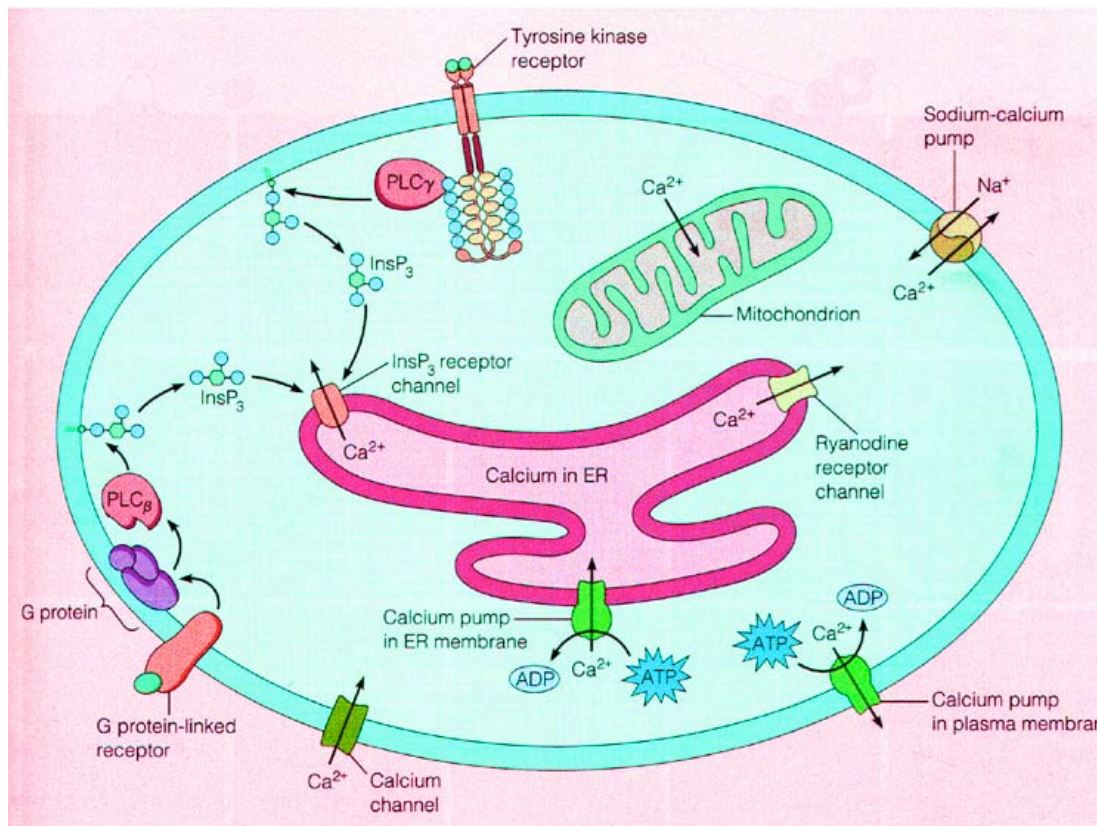


✓ Regolazioni funzioni neuronali

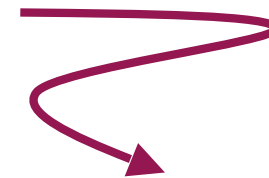
I mitocondri regolano $[Ca^{2+}]$ intracellulare

- canali Ca^{2+} uniporto
 - canali Na/Ca scambiatori
- uptake (matrice)
rilascio (cytosol)

Il potenziale di membrana guida il processo



Accumulo di Ca^{2+}
mitocondriale



MPT, swelling,
rottura delle membrane

Condizioni fisiologiche:  $[Ca^{2+}]$ intracellulare transienti
(sec-min)

Condizioni patologiche  $[Ca^{2+}]$ intracellulare persistenti

Come il Ca^{2+} uccide i neuroni?

Ca^{2+} attiva cisteina proteasi:
calpaine e caspasi
degradazione substrati
apoptosi

Ca^{2+} induce **stress ossidativo**

Alterazioni del $[Ca^{2+}]$ e neurodegenerazioni

Analisi SNC di pazienti con HD, PD, HD, e SLA indica un ruolo del $[Ca^{2+}]$ nella morte neuronale:

- ✓ Eccitotossicità in HD, PD e SLA
- ✓ Neuroni DA con molta calbindina e calretinina sono resistenti alla degenerazione nel PD
- ✓ Neuroni affetti nell' HD hanno bassi livelli di paravalbumina
- ✓ Overload di Ca mitocondriale in HD e SLA