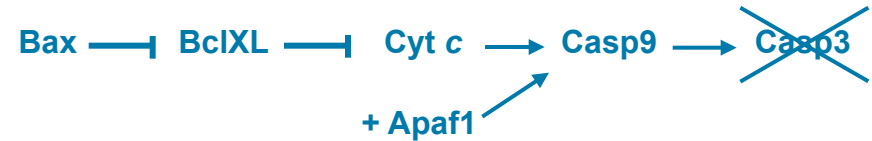


Sviluppo del sistema nervoso

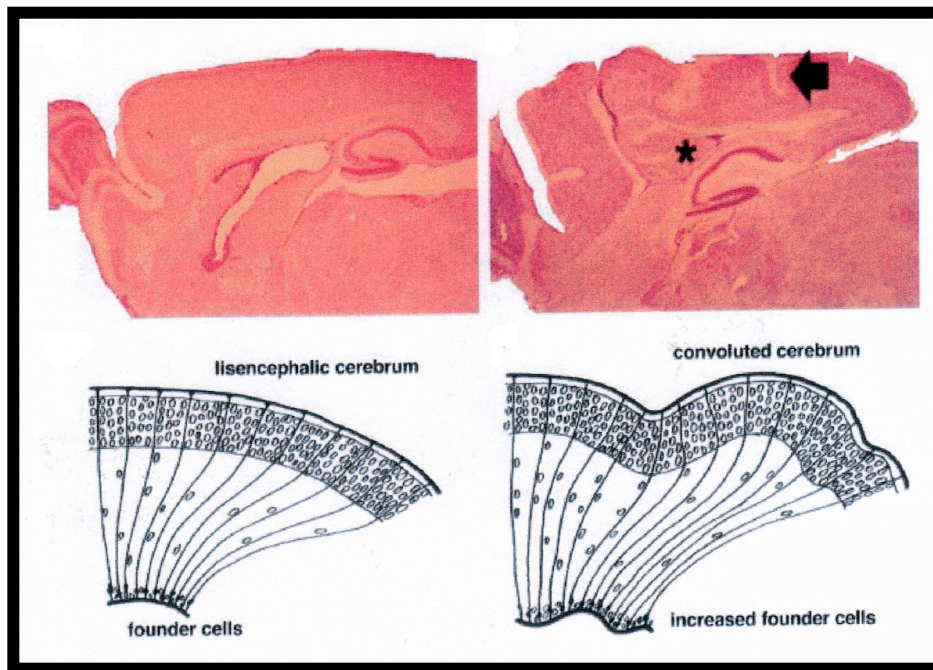
Caspase 3 Knock-out:



+/+

-/-

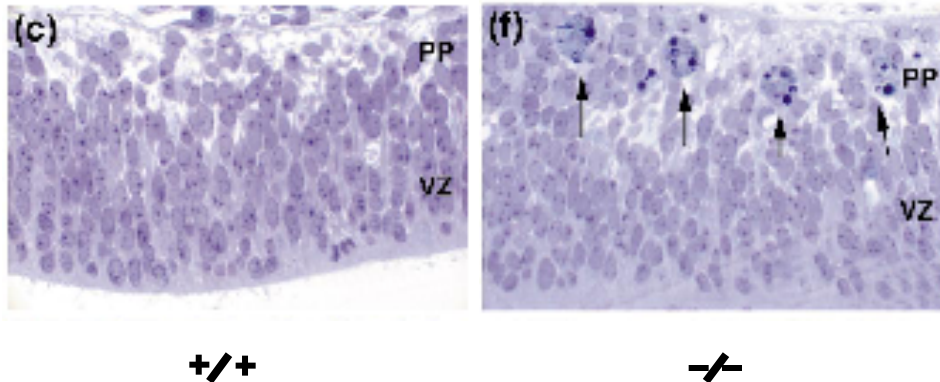
PN 16



From Roth *et al.*, 1999

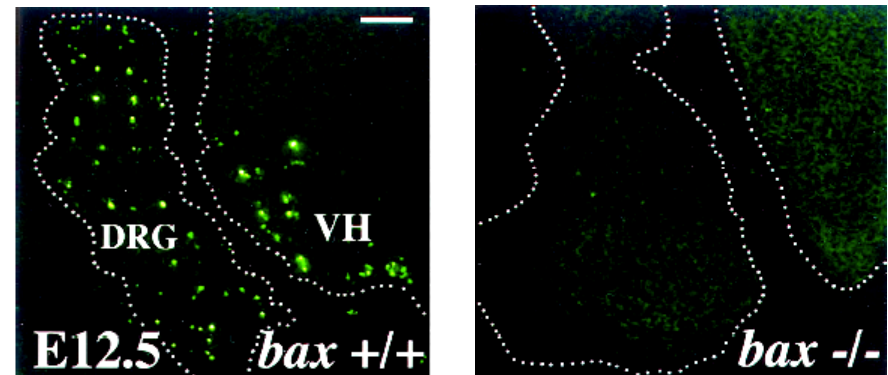
Sviluppo del sistema nervoso

BclXL Knock-out:

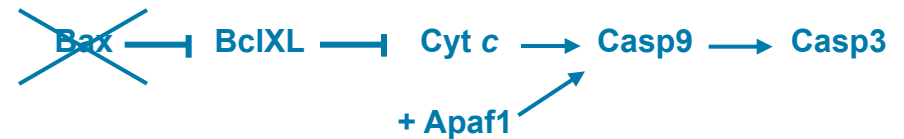
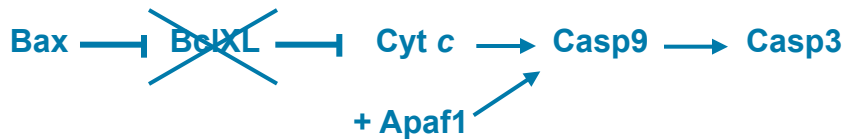


From Kuan *et al.*, 2000

Bax Knock-out:

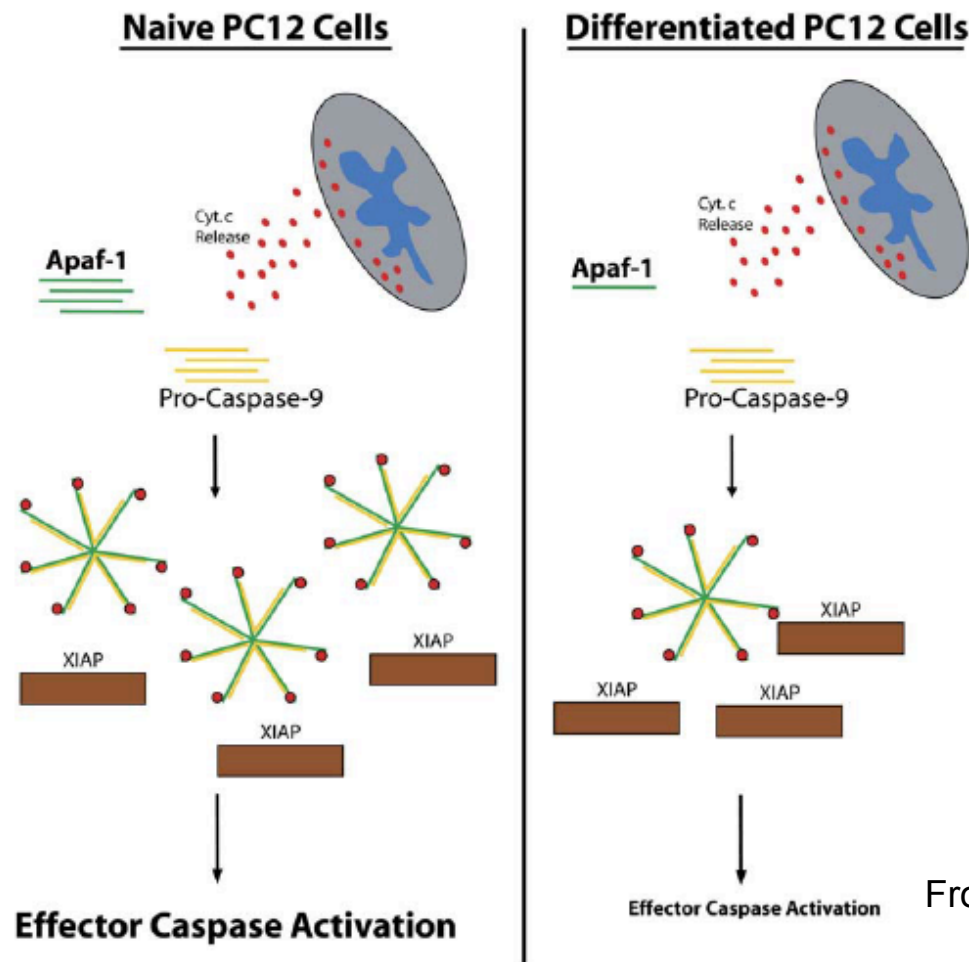


From White *et al.*, 1998



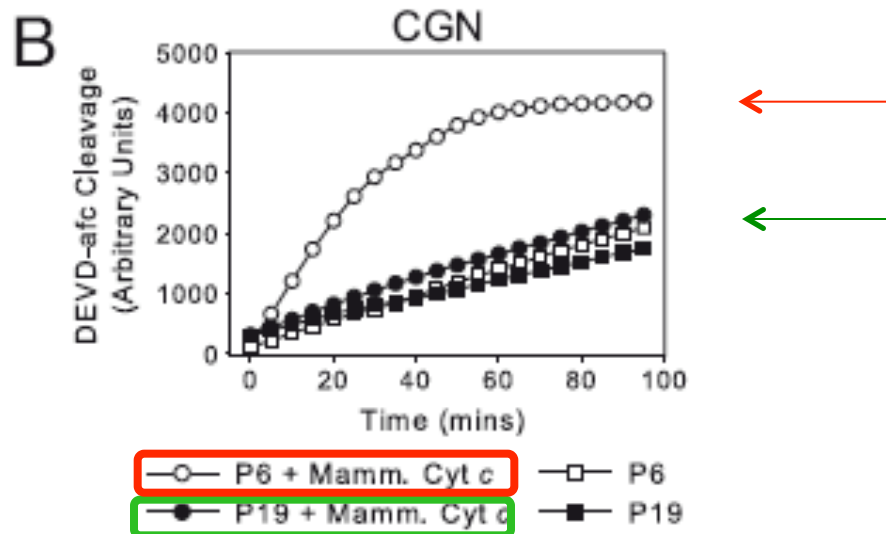
Livelli diversi di proteine apoptotiche determinano
una diversa risposta agli stimoli apoptotici:

ES. Apaf1 in Cellule progenitrici vs differenziate

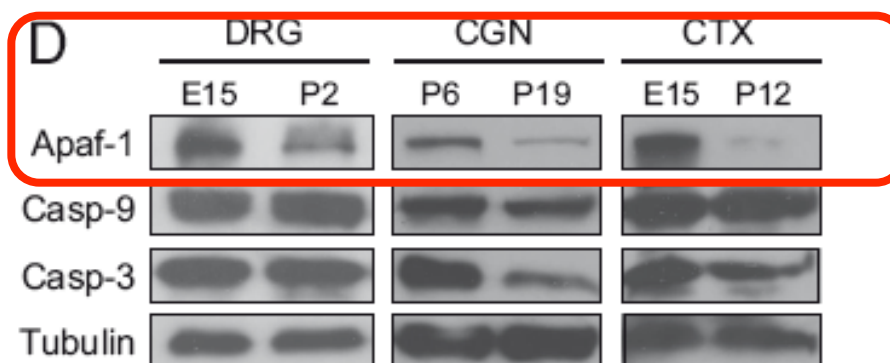


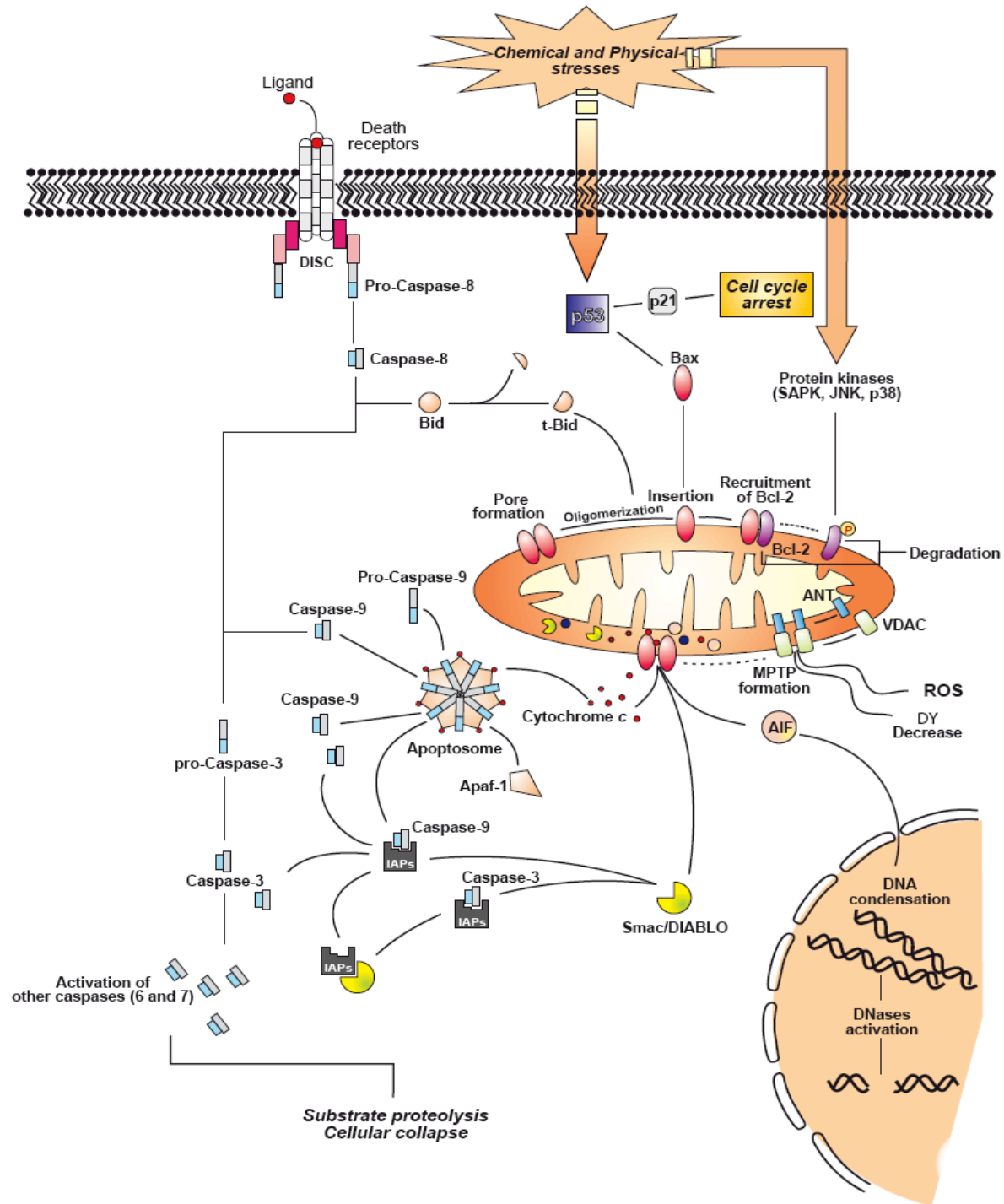
From Schafer *et al.*, 2006

L'aggiunta di cyt c **non induce** l'attivazione della casp 3 in **neuroni maturi**



La molecola chiave che determina questa differenza è **APAF1**, presente a diversi livelli nei **precursori neuronali** e nei **neuroni differenziati**





Apoptosi e danno al DNA

Quando la cellula ha il DNA danneggiato:

1. Attua meccanismi di riparo
2. Se il danno è irreparabile o il sistema di riparo non funziona la cellula va in apoptosi

Esistono vari sistemi di riparo del danno al DNA, a seconda del tipo di danno.

Se il danno è caratterizzato dalla rottura del doppio filamento (DSB), due sono i processi che possono essere attivati:

1. Ricombinazione omologa (HR)

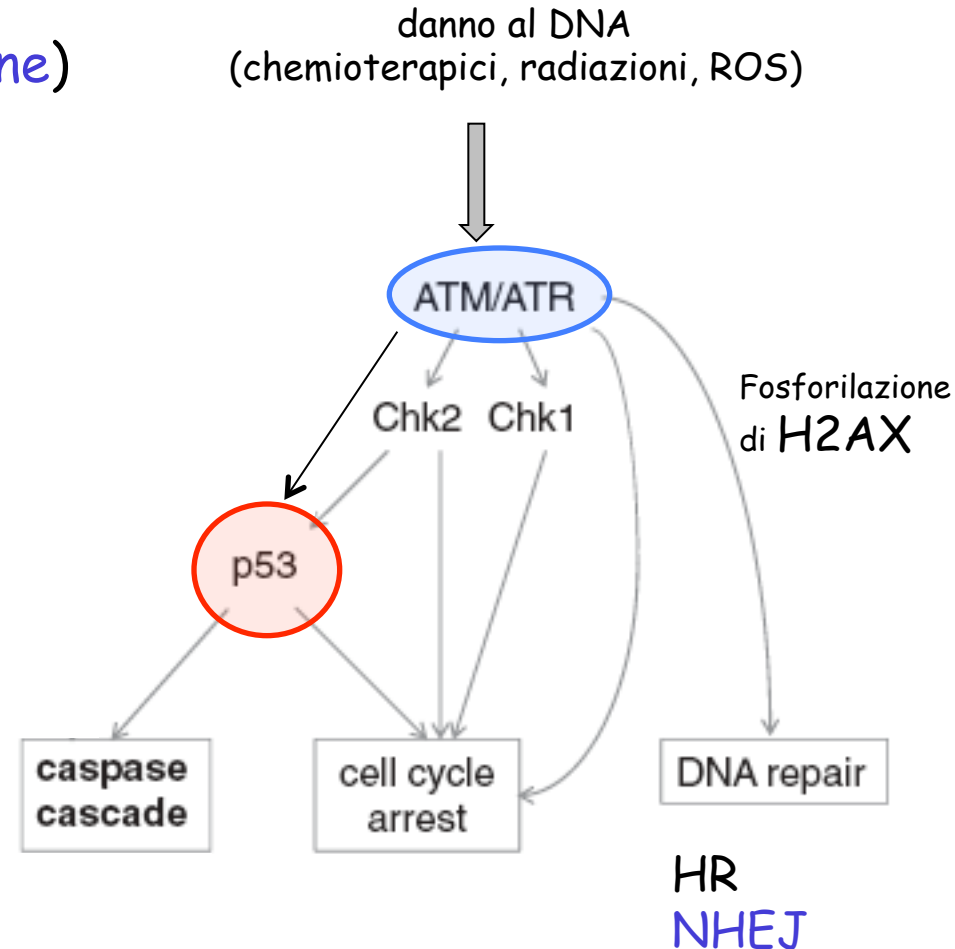
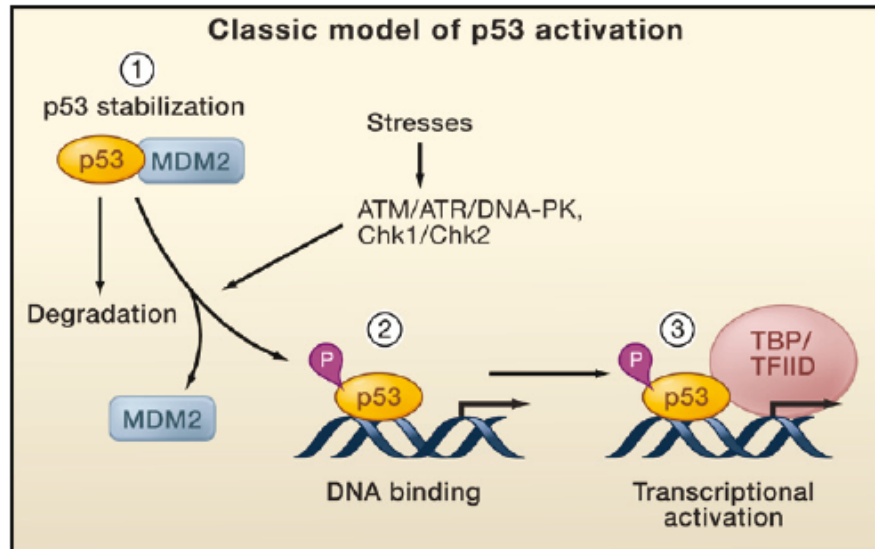
2. Ricombinazione non omologa (NHEJ)

(il pathway più usato poichè non prevede la presenza del cromatide fratello e può essere utilizzato durante tutto il ciclo cellulare)

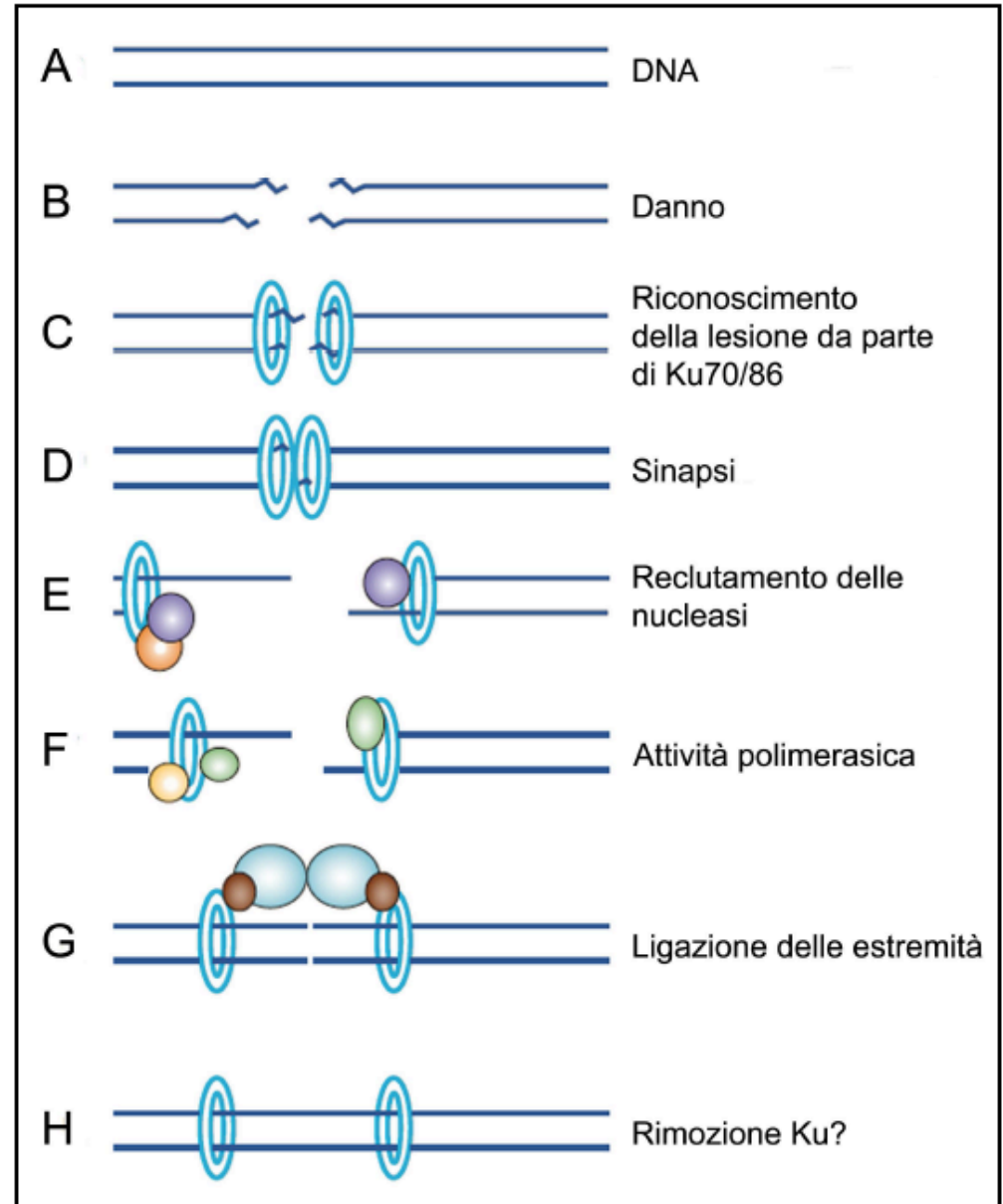
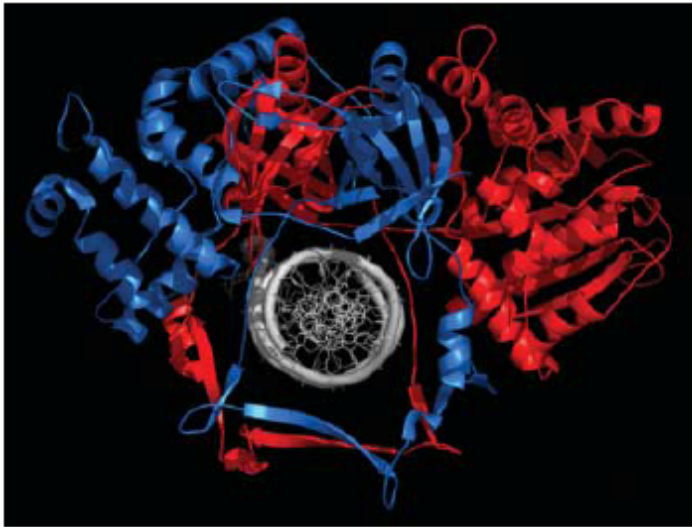
p53: il "guardiano del genoma"

p53 subisce modificazioni post-traduzionali (tipo **fosforilazione**) che ne aumentano i livelli e l'attività trascrizionale

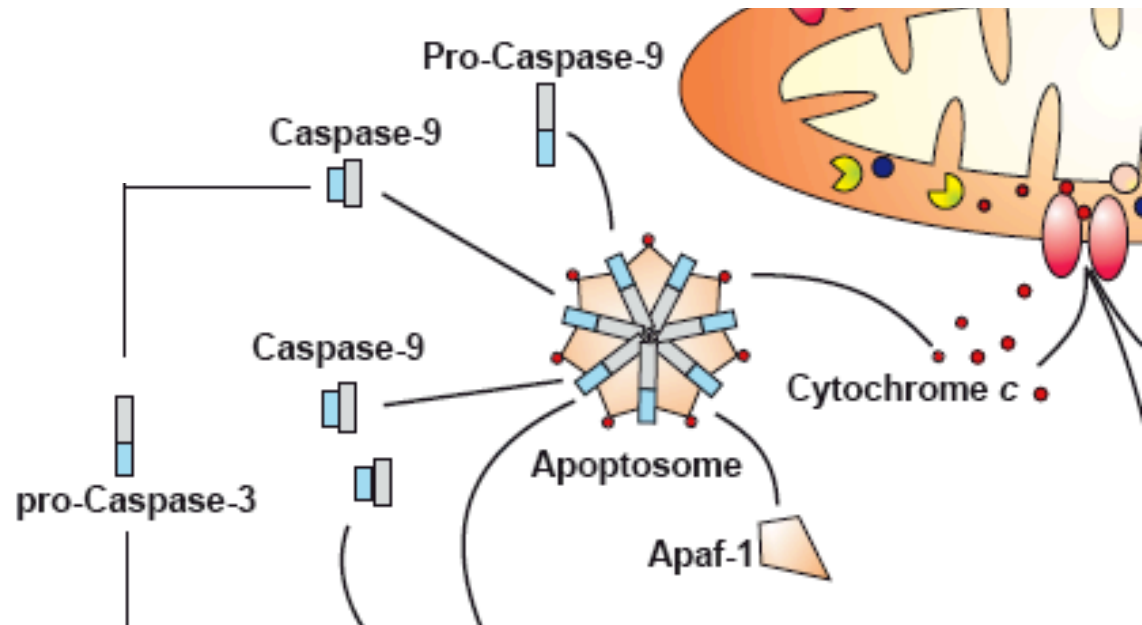
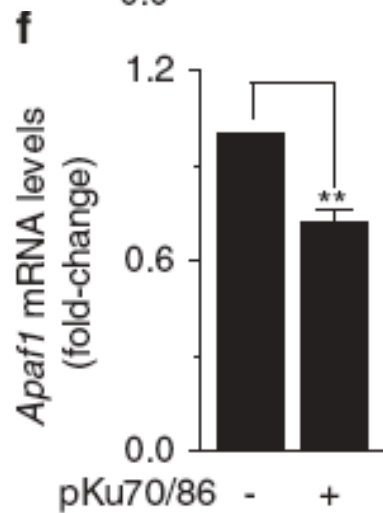
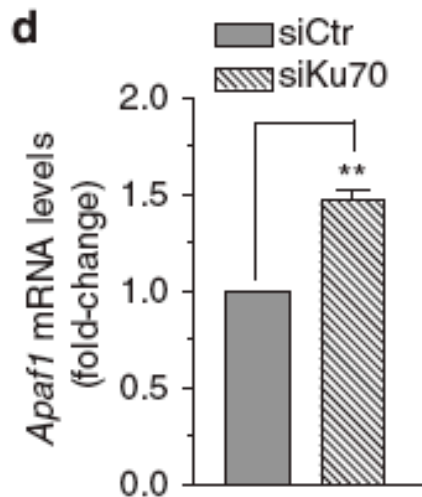
p53 attiva la trascrizione di vari geni apoptotici (Noxa, PUMA, Bax, Bid, Apaf1)



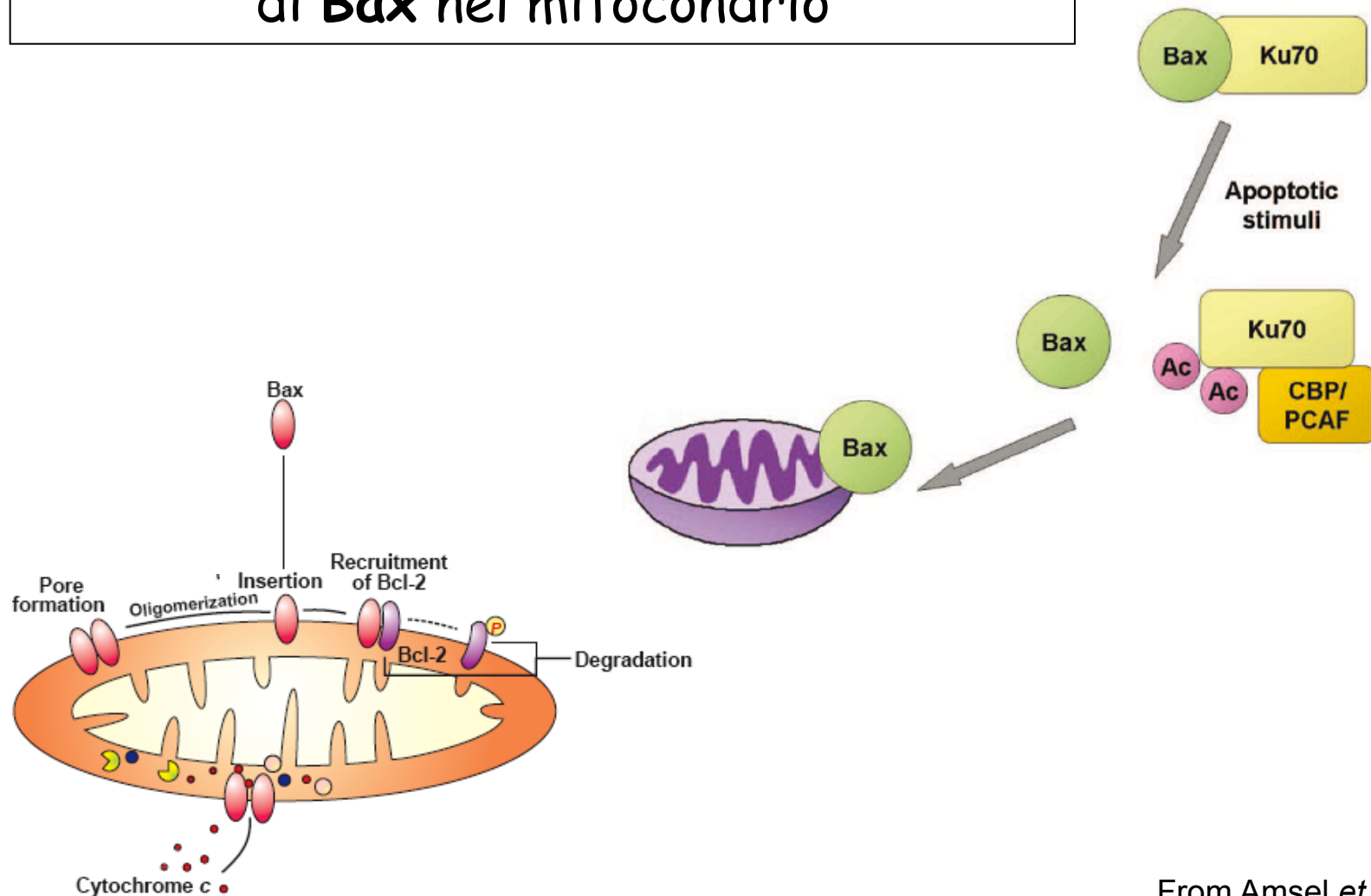
Ku70/86: la proteina di riparo del danno al DNA (NHEJ)



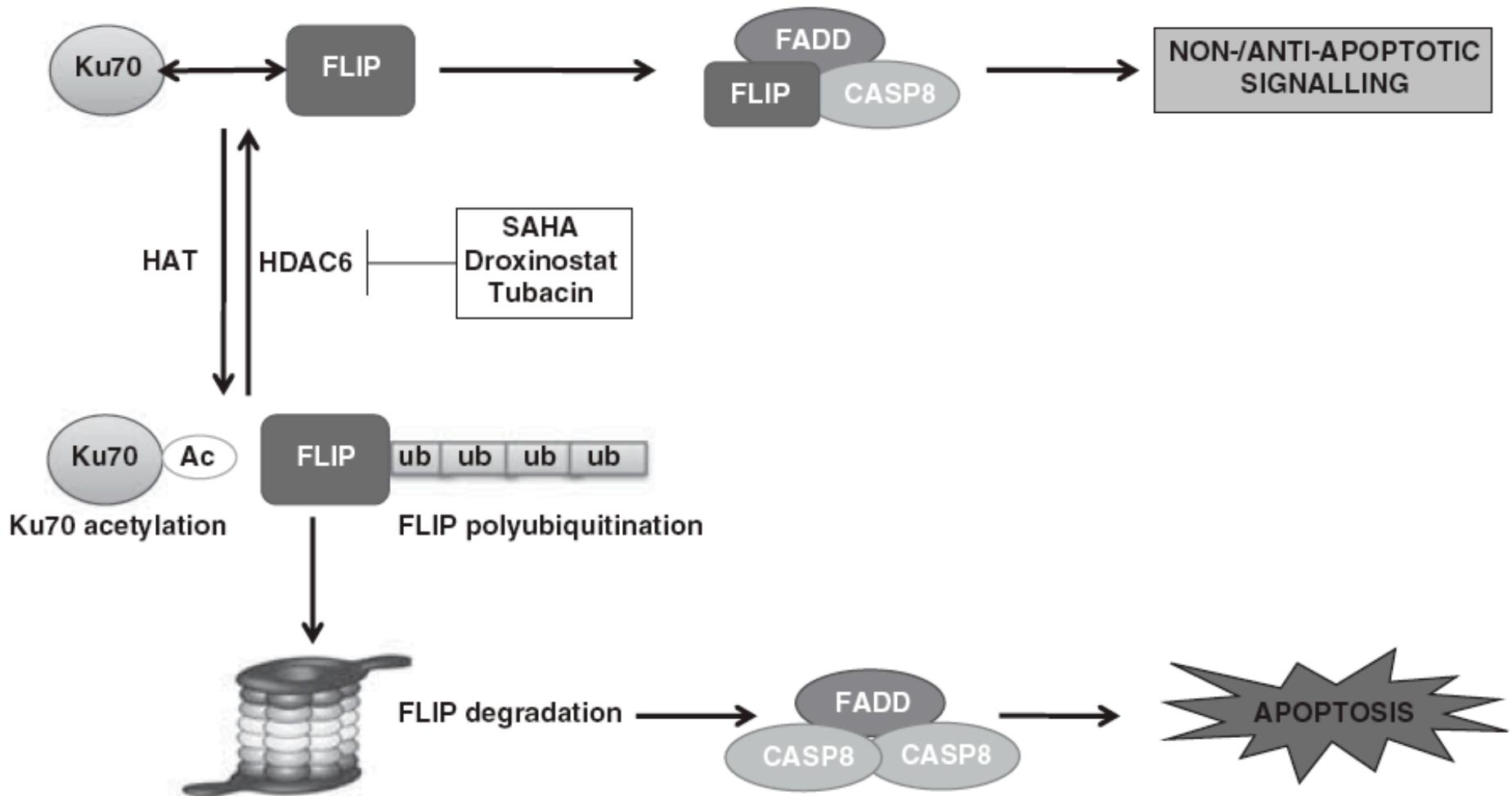
Ku70/86 reprime l'espressione del gene **Apaf1**



Ku70 citosolico inibisce la traslocazione di Bax nel mitocondrio



Ku70 citosolico inibisce l'attivazione della Caspasi 8 stabilizzando FLIP



Problem solving:

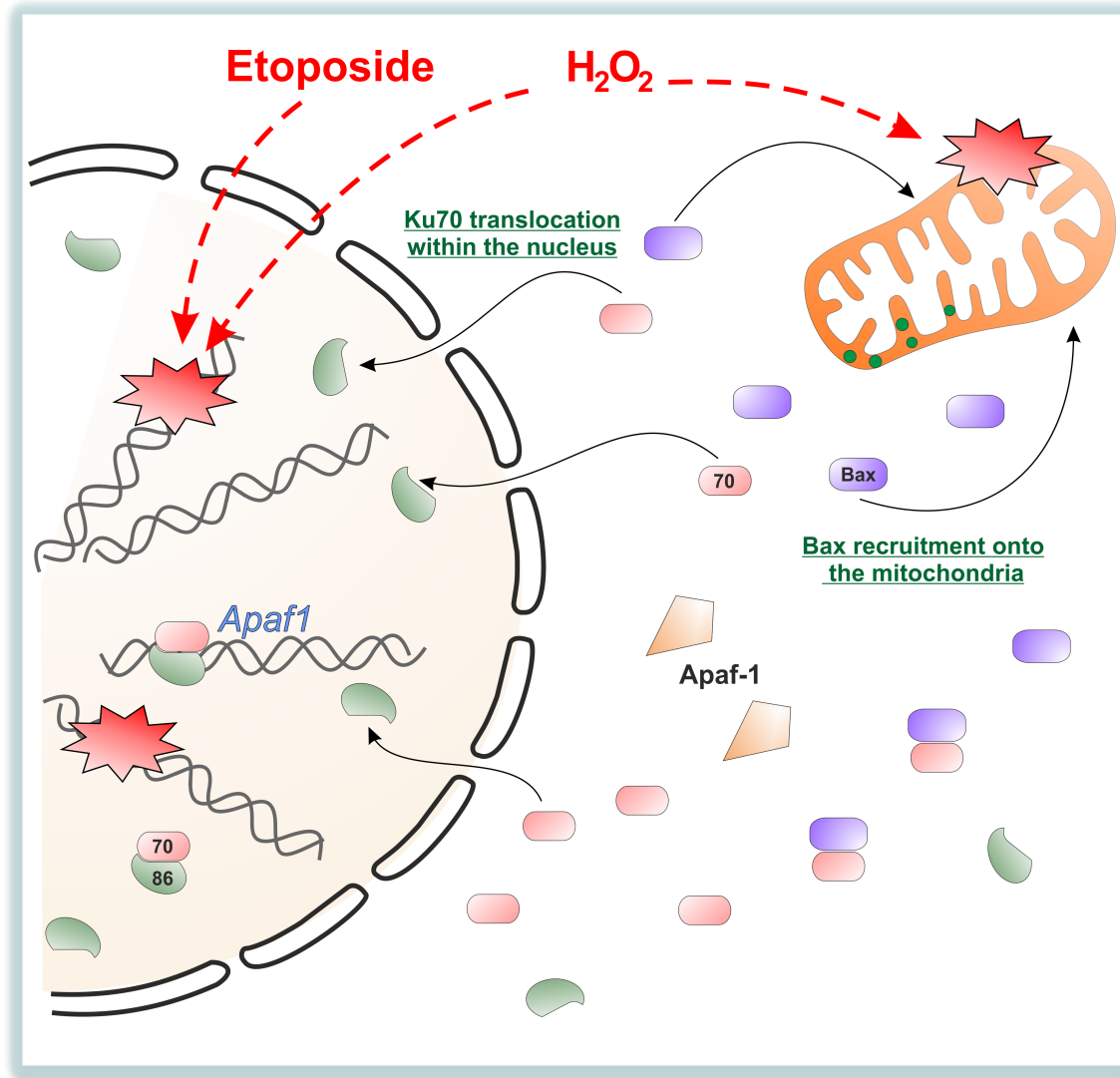
a) il DNA è danneggiato in cellule precursori neuronali....

b) osservo morte cellulare apoptotica solo molto tempo dopo....

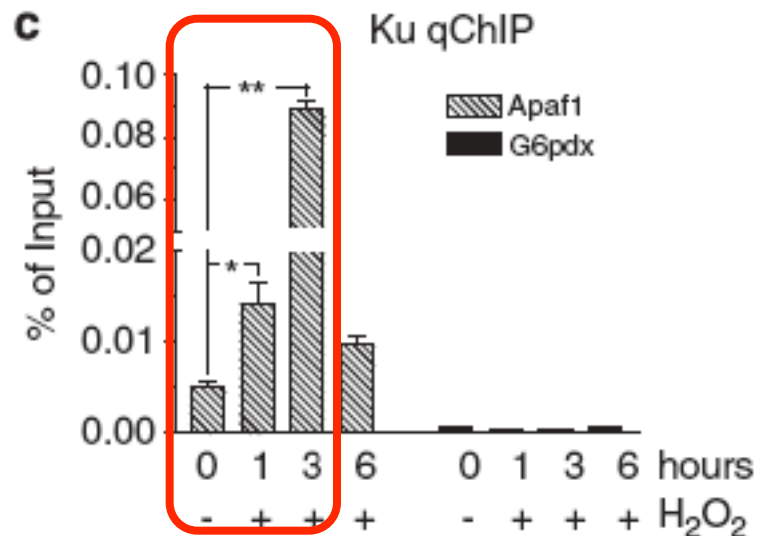
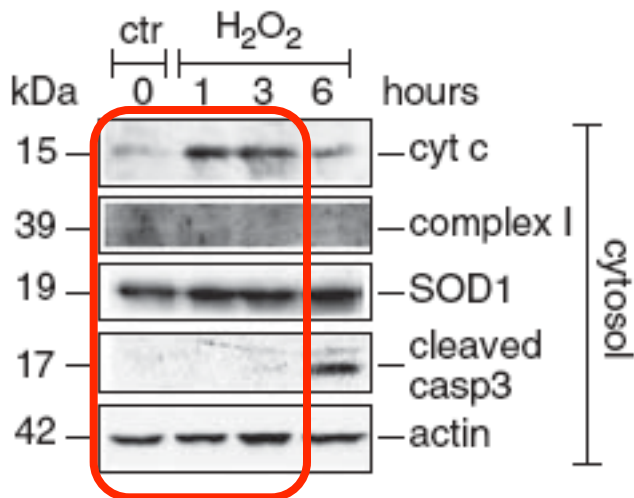
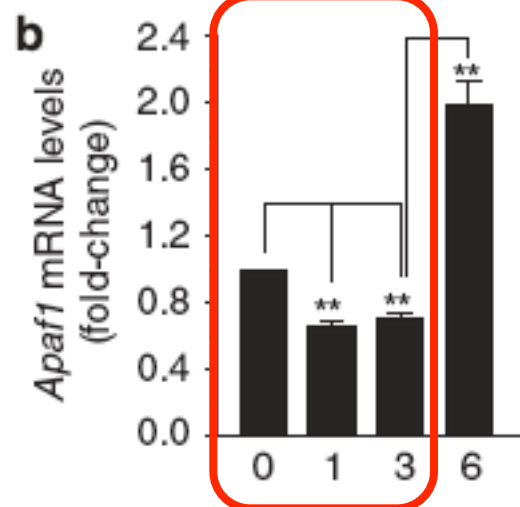
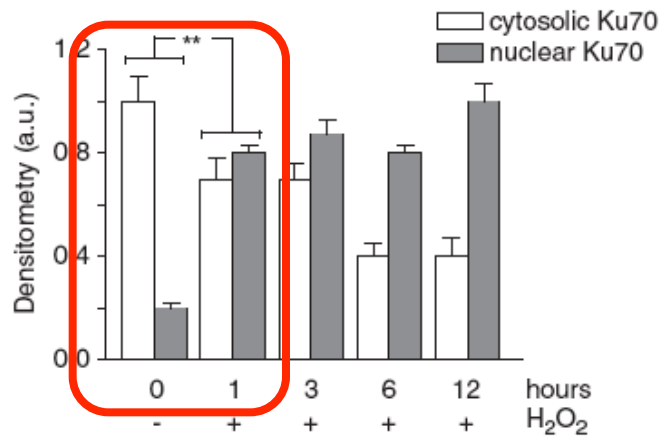
QUALI SONO I MECCANISMI CHE DETERMINANO TALE DESTINO CELLULARE?

E QUALI LE MOLECOLE COINVOLTE?

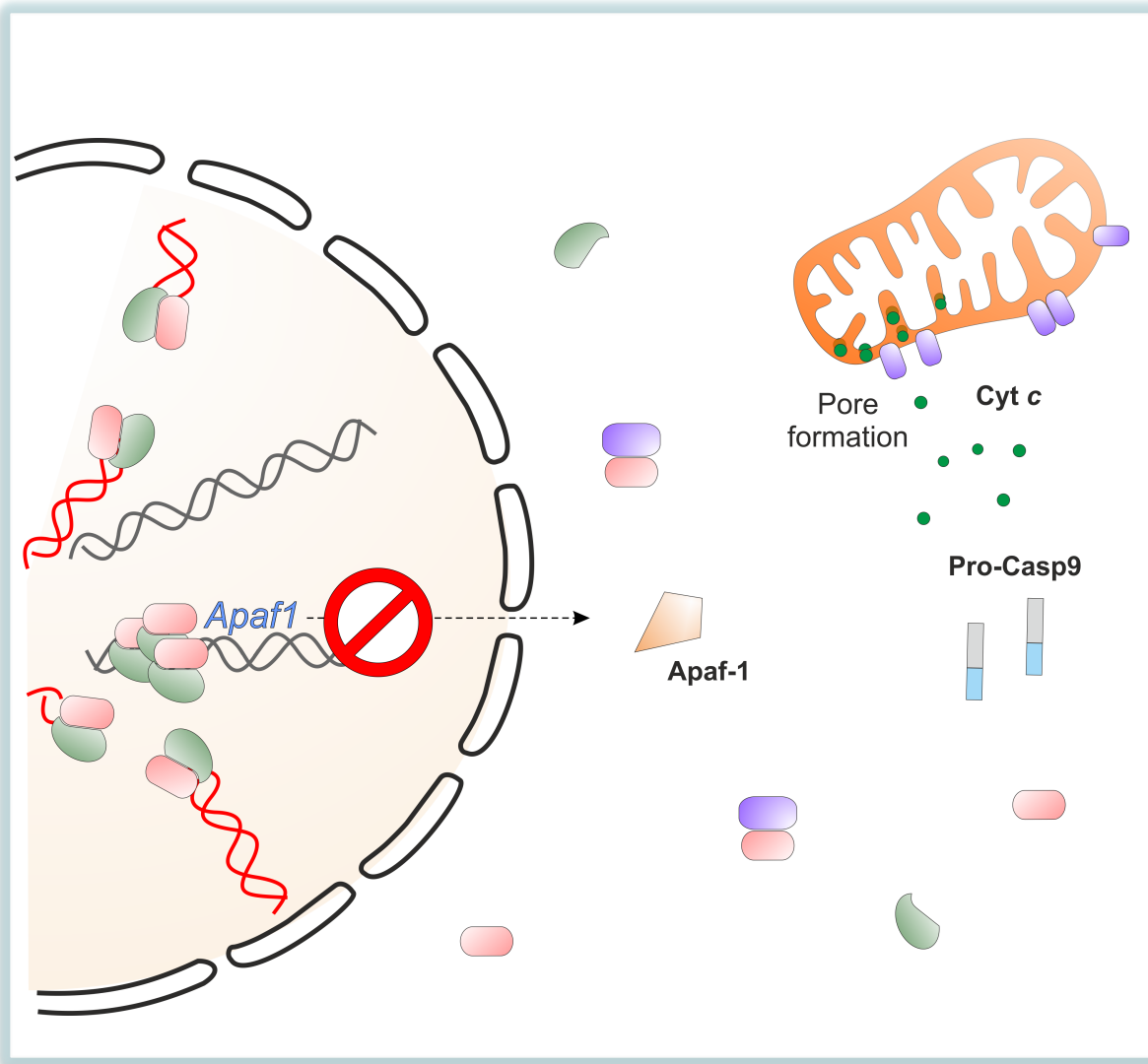
A seguito dell'induzione del danno al DNA:



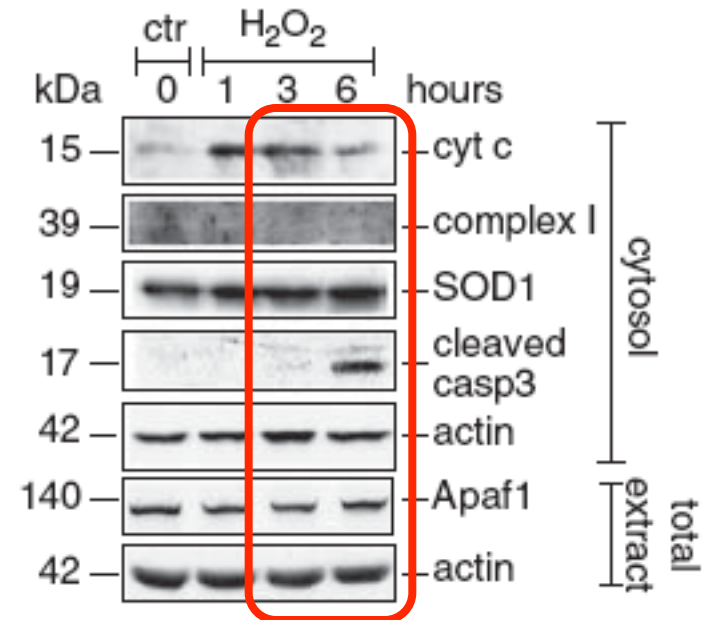
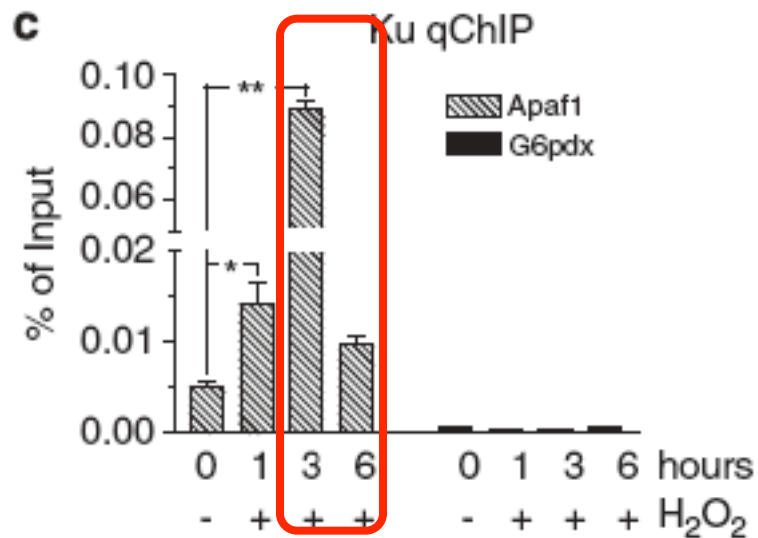
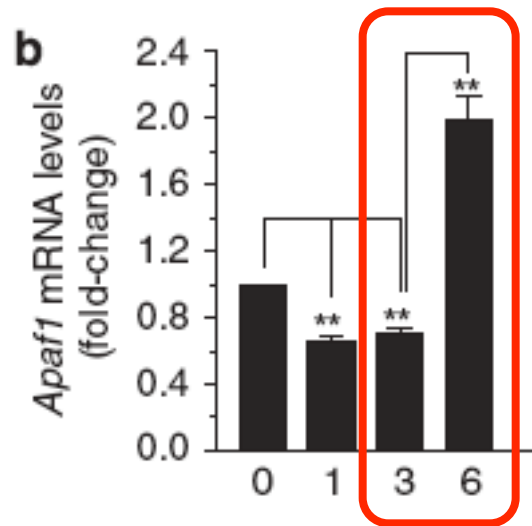
I° fase: risposta di sopravvivenza:
Ku70 si accumula nel nucleo
Ku70/86 reprime la trascrizione di Apaf1



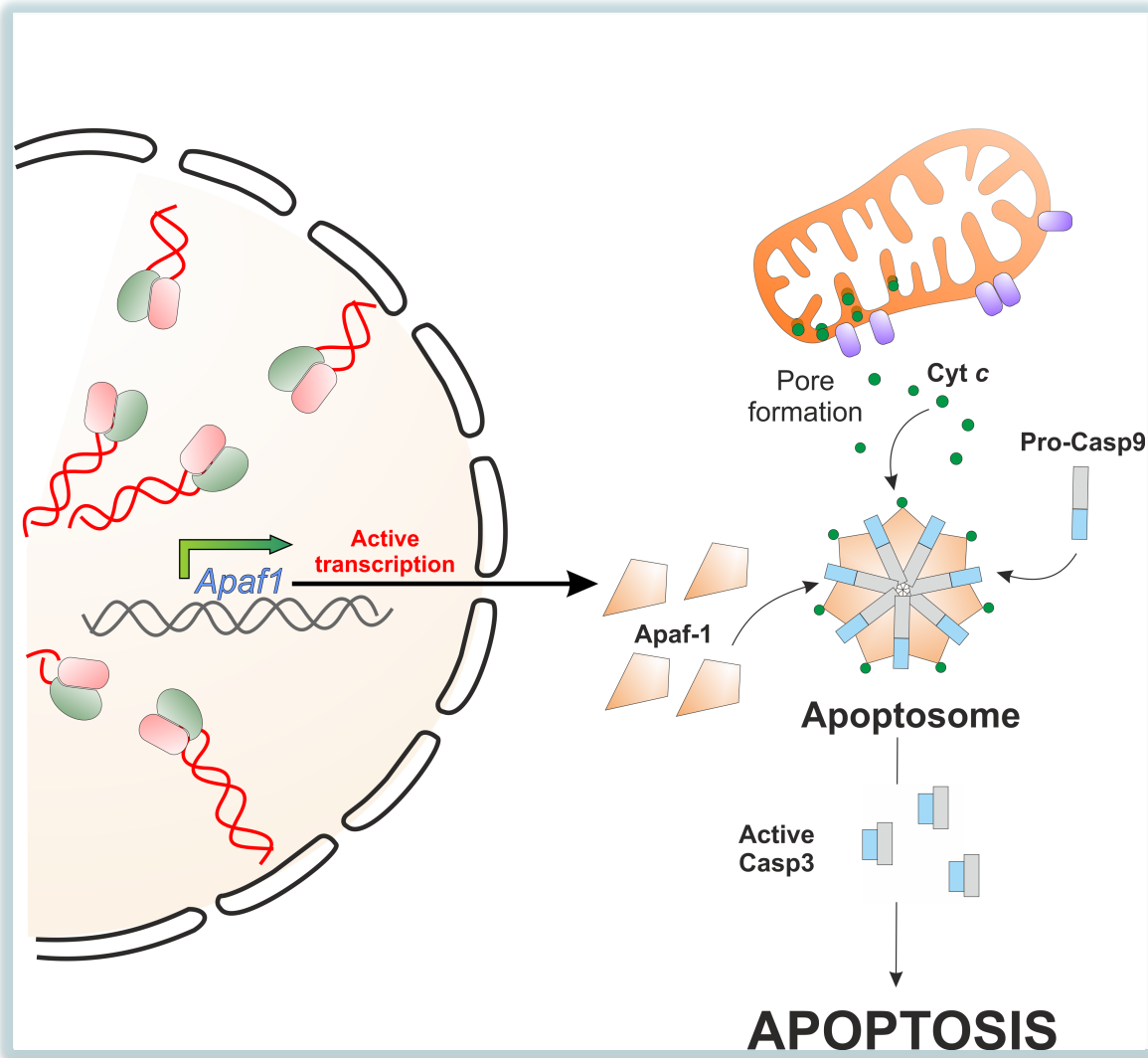
I° fase: risposta di sopravvivenza
Ku70/86 reprime l'apoptosi



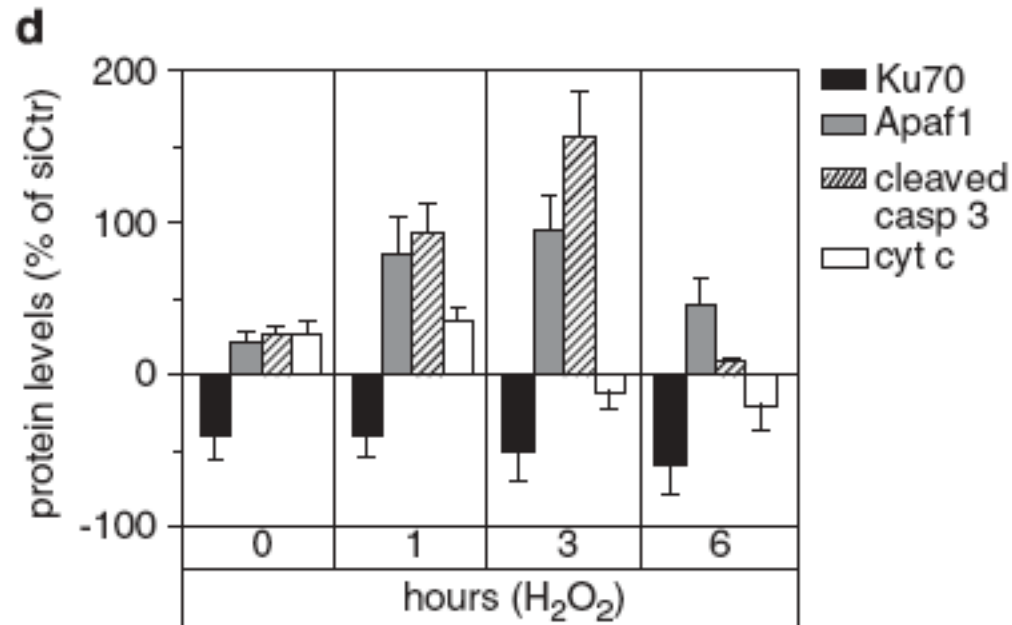
II° fase: morte cellulare apoptotica



II° fase: morte cellulare apoptotica



La modulazione negativa di Ku70/86 induce apoptosi a tempi più brevi



Referenze reviews:

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Nature Reviews. Mol Cell Biol 9, 231-241

2. Mitochondria and cell death: outer membrane permeabilization and beyond

S.W.G. Tait and D.R. Green (2010)

Nature Reviews. Mol Cell Biol 11, 621-632

3. Programmed cell death in animal development and disease

Y. Fuchs and H. Steller (2011)

Cell, 147, 742-758

4. Expanding roles of programmed cell death in mammalian neurodevelopment

D. De Zio, L. Giunta, M. Corvaro, E. Ferraro and F. Cecconi (2005)

Semin Cell Dev Biol 16, 281-294