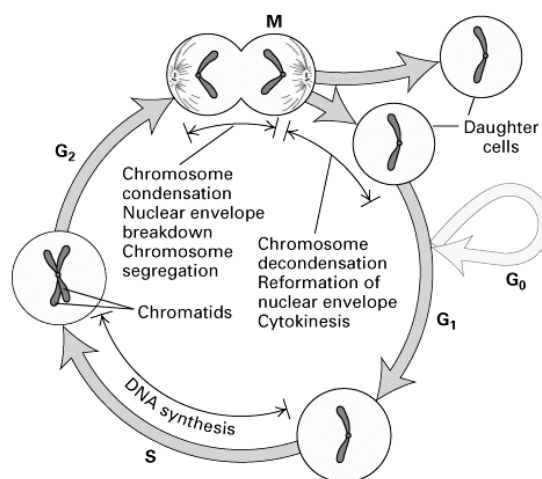
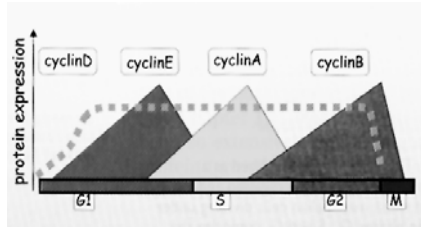


De-regolazione del ciclo cellulare nei tumori umani

Il ciclo cellulare induce la duplicazione delle
cellule attraverso un'ordinata serie di eventi



Le cicline oscillano durante le varie fasi del ciclo cellulare



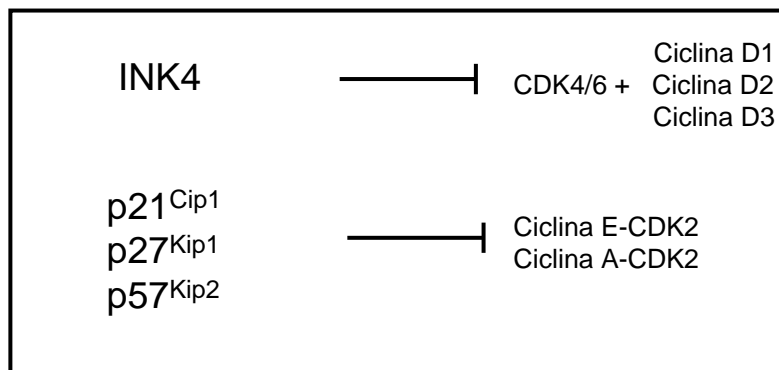
Tipi di cicline e di chinasi che regolano le varie fasi del ciclo cellulare

G1	ciclina D/Cdk- 4,6
G1/S	ciclina E/ Cdk-2
S	ciclina A/Cdk-2
M	ciclina B/Cdk-1

Durata della varie fasi del ciclo cellulare

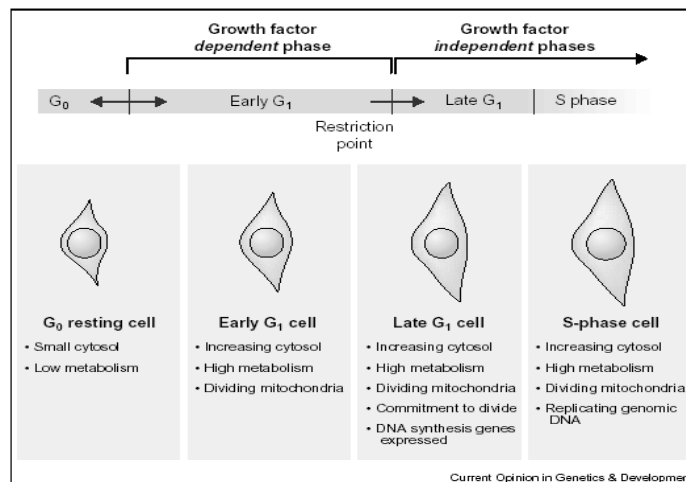
Fasi del ciclo	Durata (h)
G1	10
S	7.5
G2	3.5
M	1.0

Inibitori che controllano il ciclo cellulare

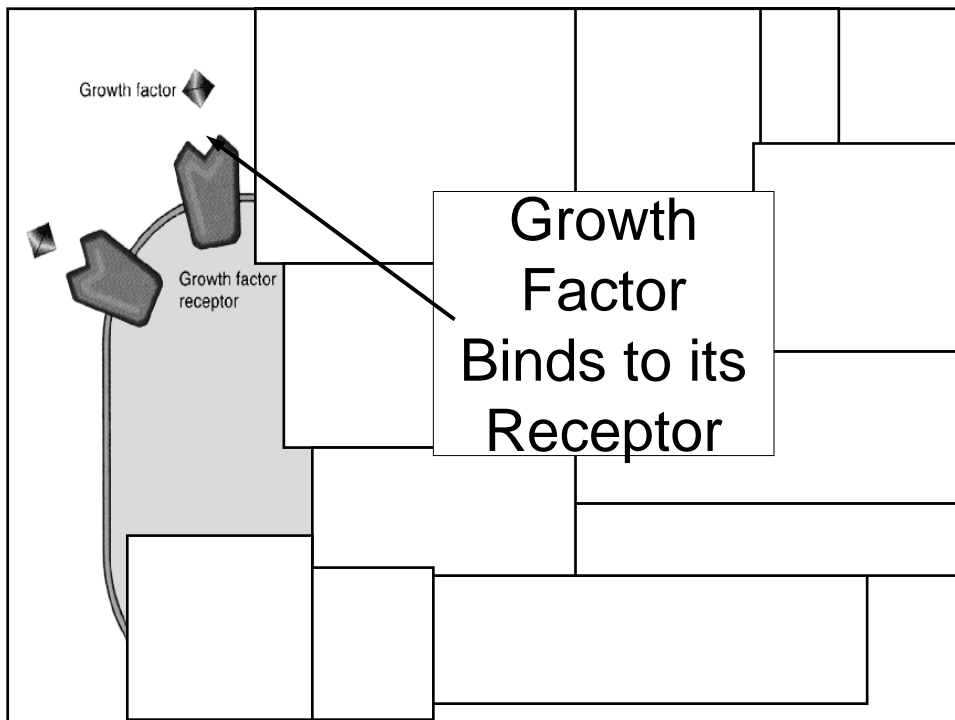


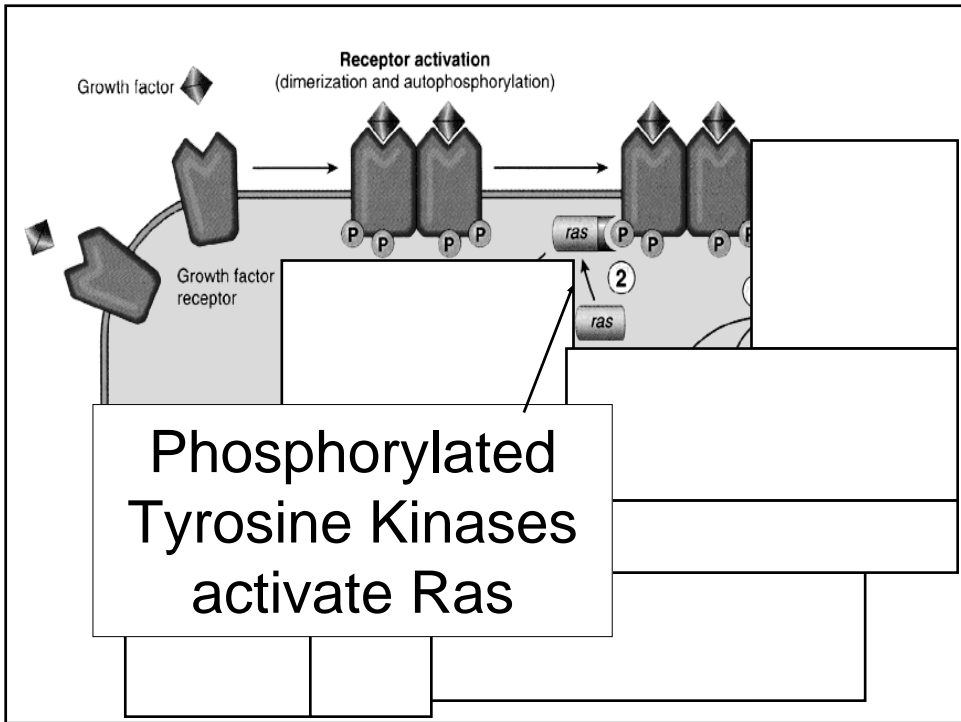
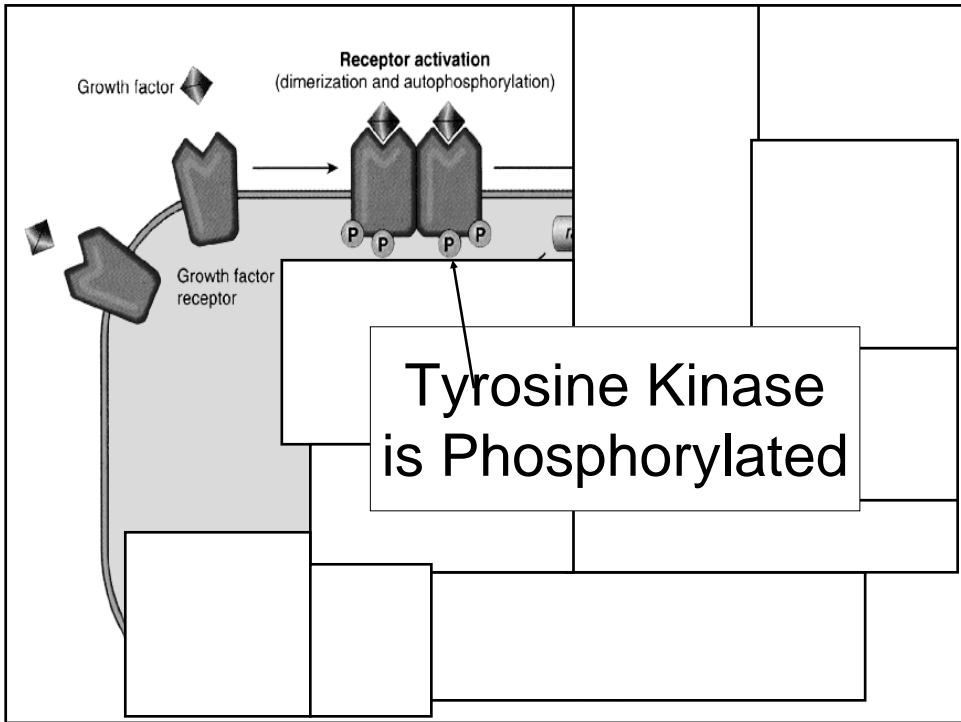
La fase G1 è l'intervallo in cui le cellule rispondono agli stimoli extracellulari e decidono se duplicare il DNA e dividersi, o uscire dal ciclo ed entrare in uno stato di quiescenza (G0)

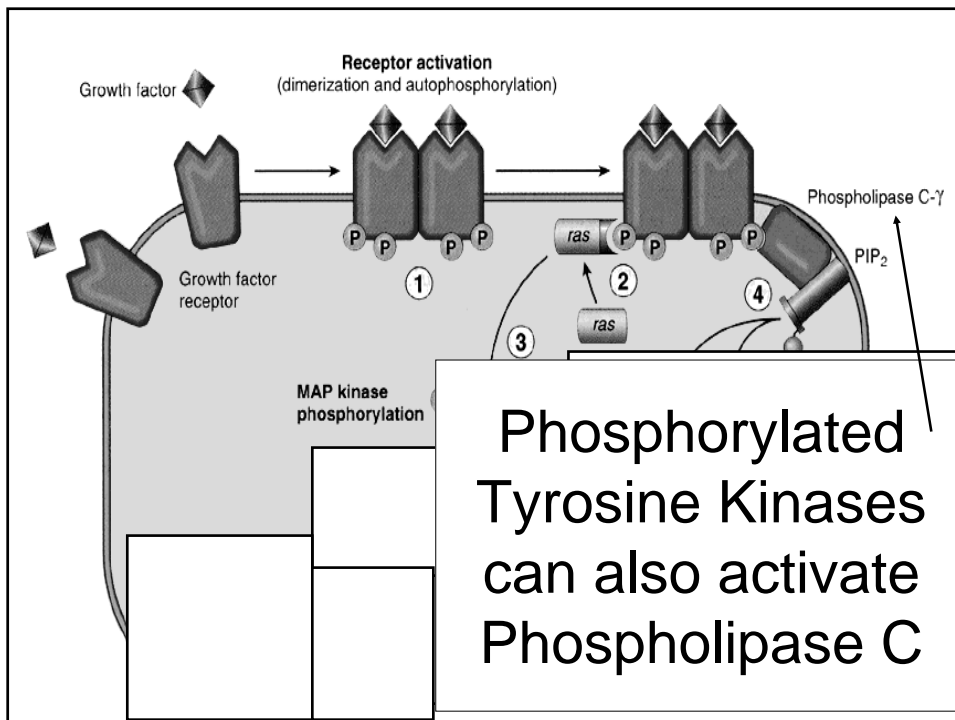
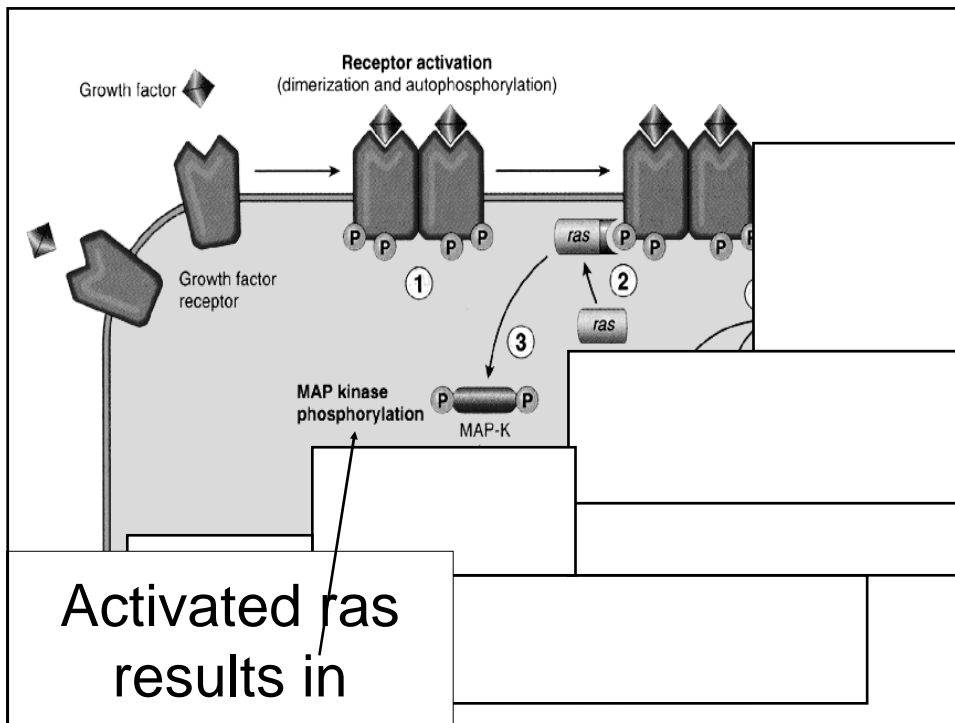
Punto di restrizione

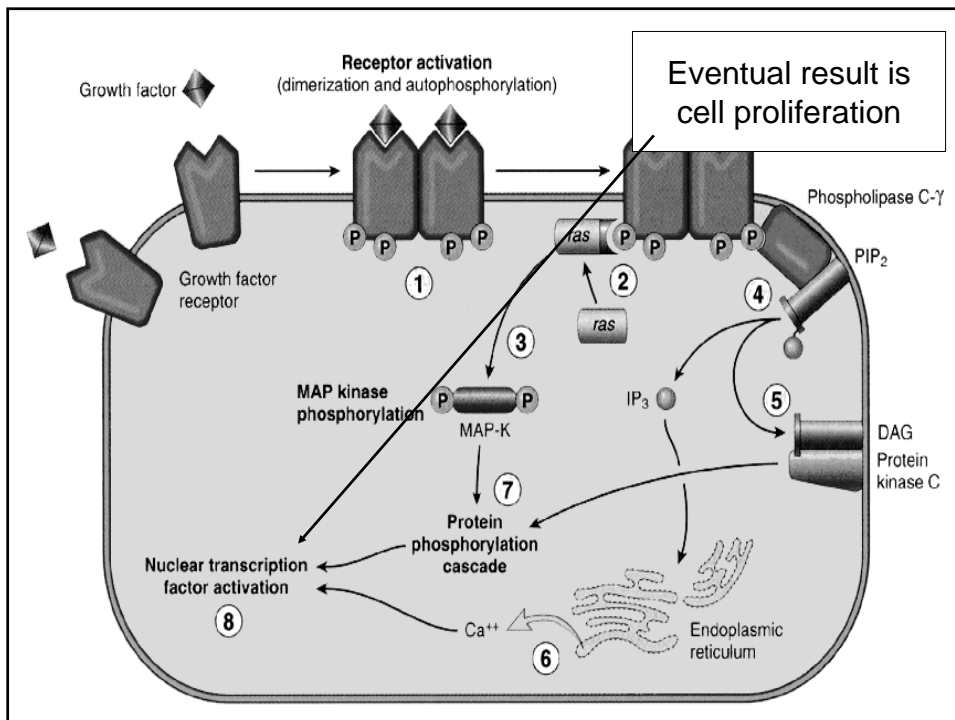
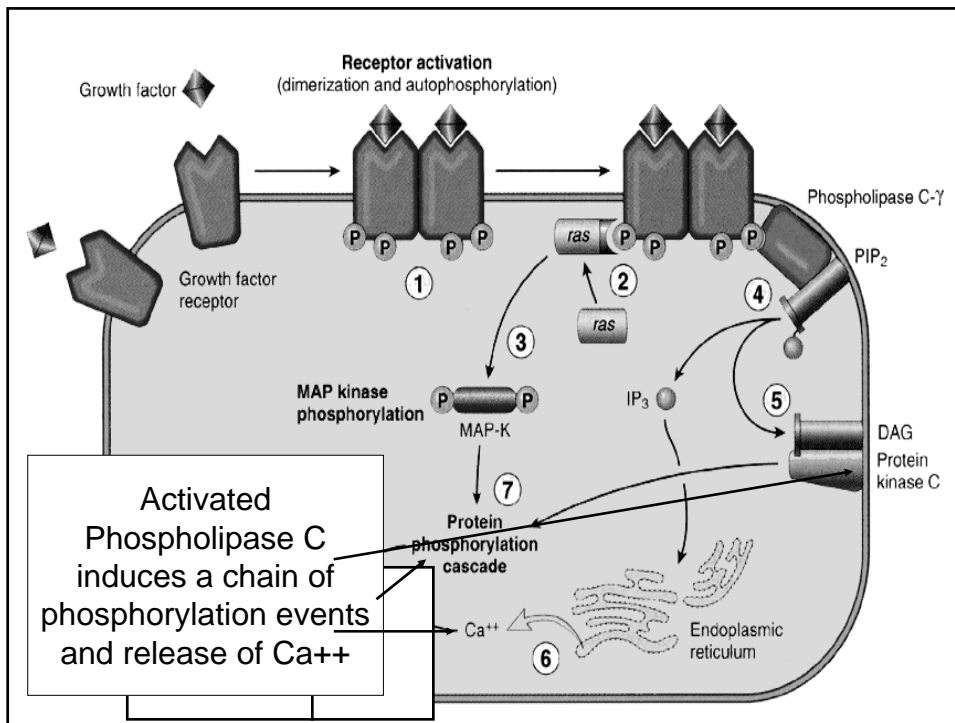


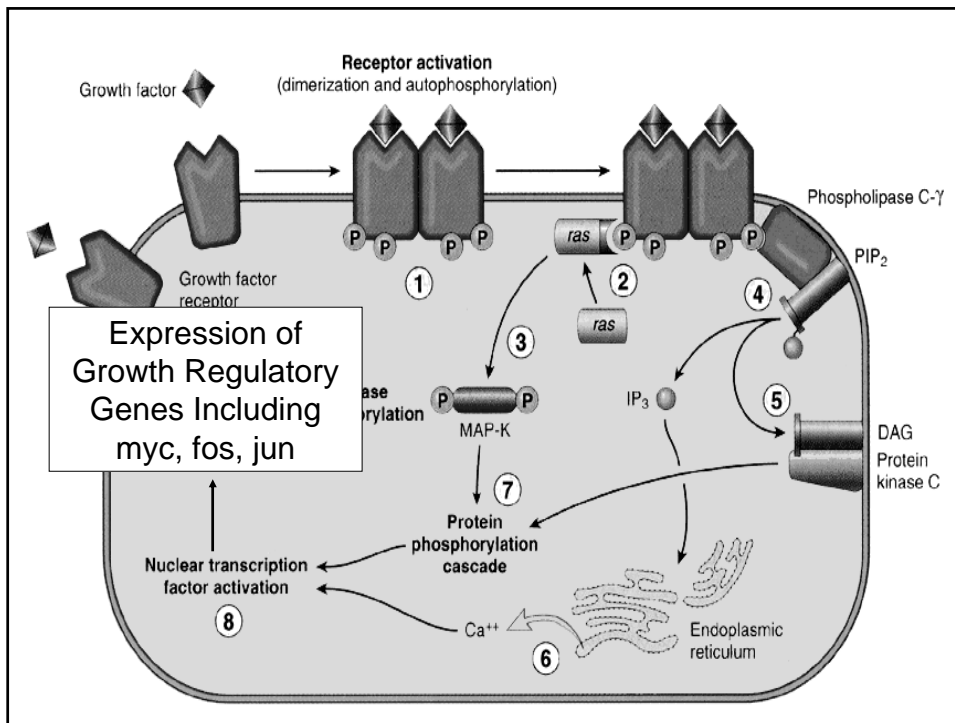
I fattori di crescita e la matrice extracellulare controllano il punto di restrizione mediante l'attivazione delle vie di trasduzione dei segnali



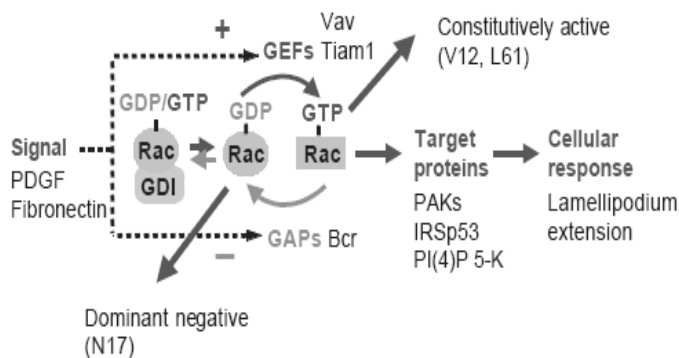






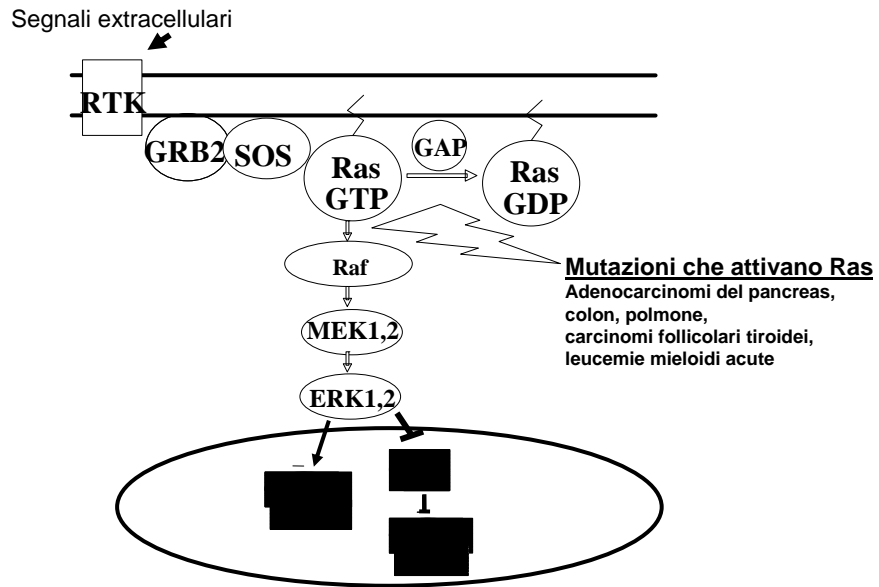


Meccanismi che regolano l'attività delle piccole proteine leganti il GTP

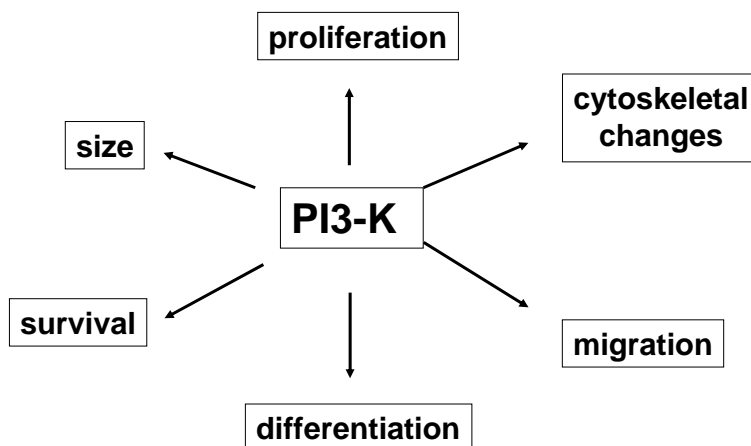


da A. Ridley, *J. Cell Sci.* 114, 2001

L'attivazione di Ras indotta dai fattori di crescita controlla il ciclo cellulare



Cellular actions controlled by PI3-K

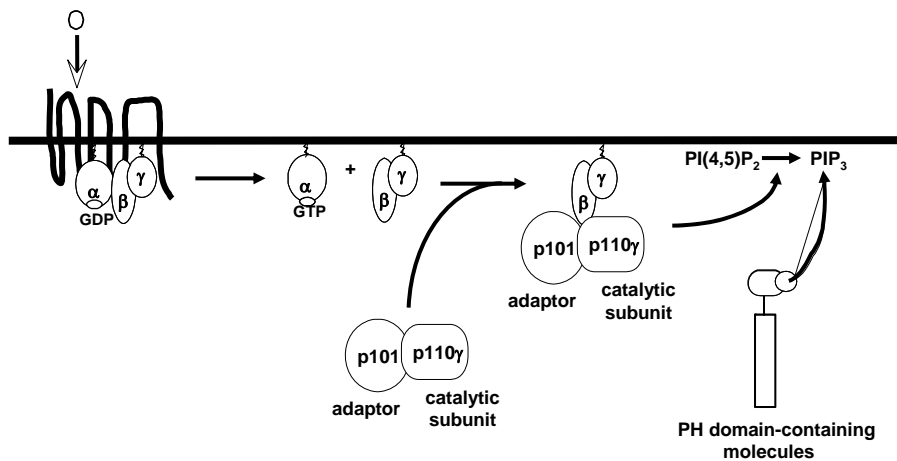


Classi di PI3-chinasi

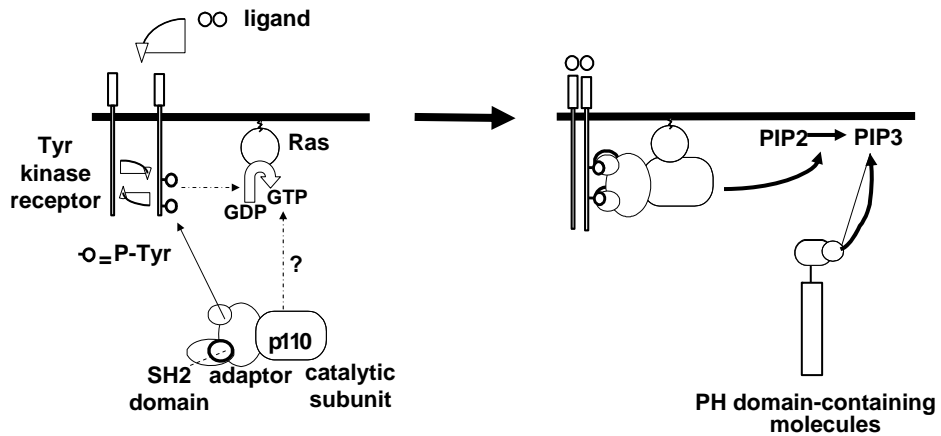
PI3K type	Subunits		Distribution	Lipid product <i>in vivo</i>	
	Catalytic	Regulatory			
I	A	p110 α β δ ¹	p55-p85 ¹	All broad ¹	PtdIns(3,4,5)P ₃
	B	p110 γ ¹	p101	Predominantly leukocyte	PtdIns(3,4,5)P ₃
II		C2 α β γ ²	?	Broad ¹	PtdIns3P
III		hVps34p ³	p150	Broad	PtdIns3P

da Stephens et al. *Curr. Opin. Cell Biol.* 2002

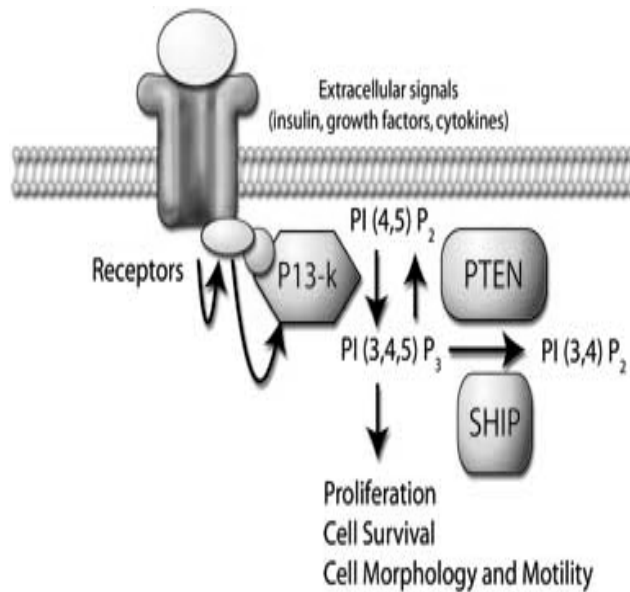
activation of p110 γ (class IB)



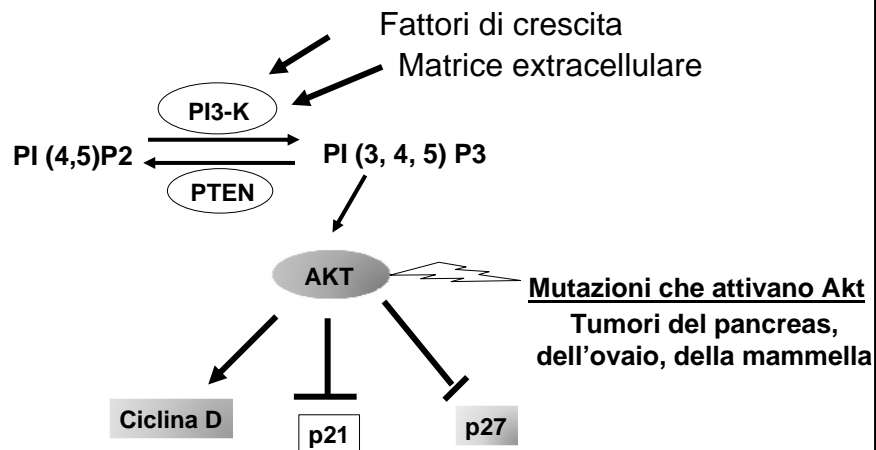
Activation of Tyr kinase-linked PI3-Ks (class IA)



Regolazione dell'attività di PI3-chinasi

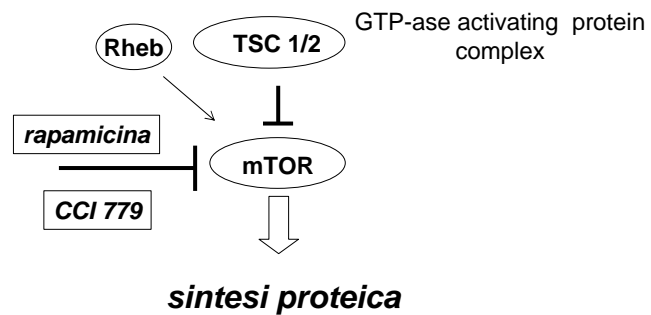


L'attivazione di PI3-chinasi controlla il ciclo cellulare

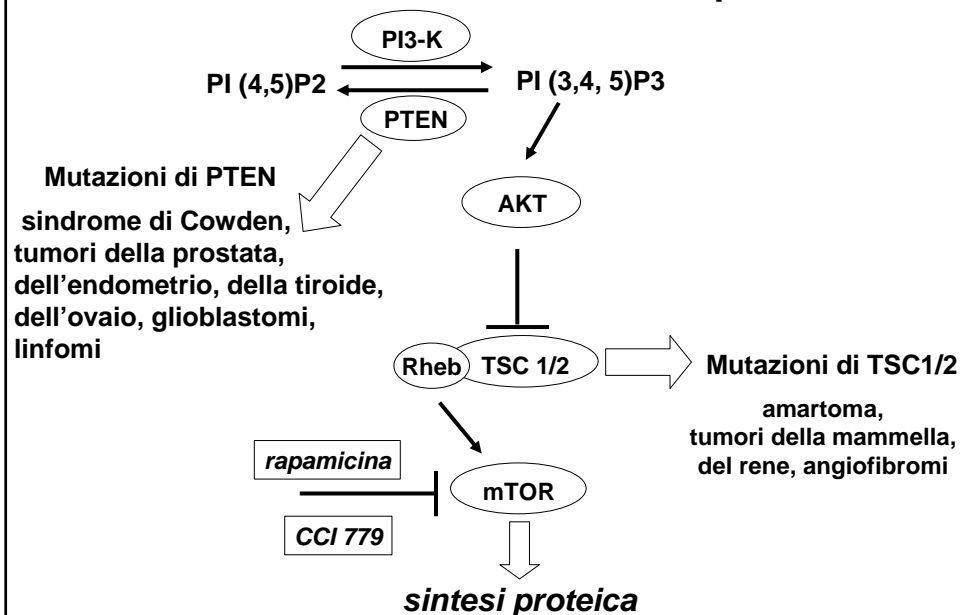


PI3-K/Akt/mTOR signaling also influences protein synthesis rates by activating S6K, which phosphorylates the 40S ribosomal subunit and leads to increased translation of mRNAs

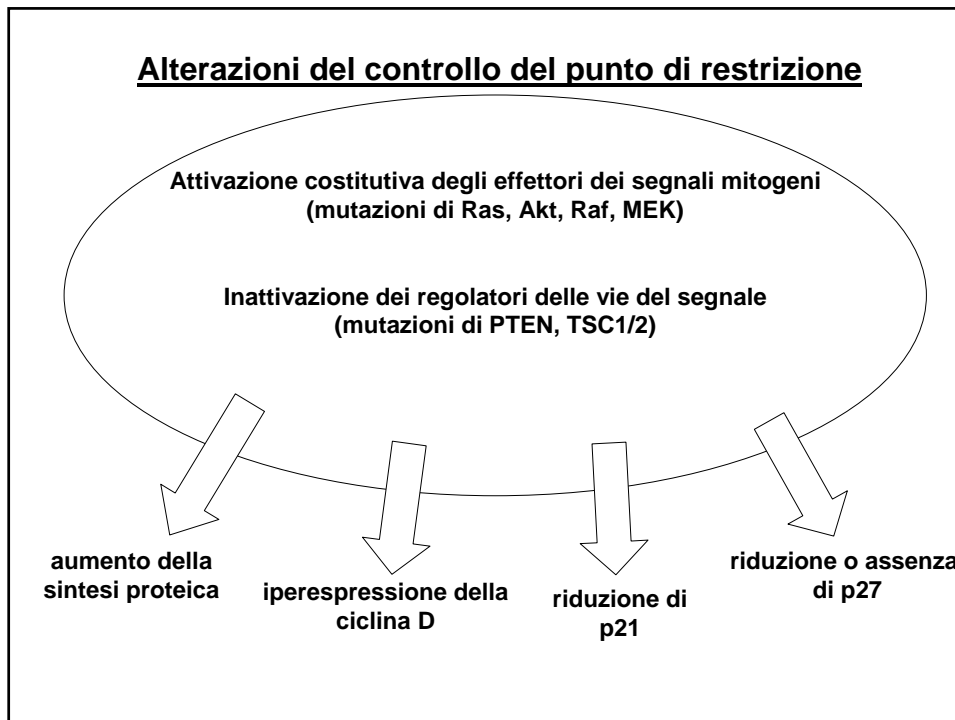
Regolazione della sintesi proteica da parte del complesso TCS 1/2



PI3-K nel controllo della sintesi proteica



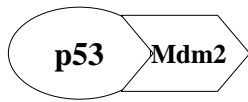
Alterazioni del controllo del punto di restrizione



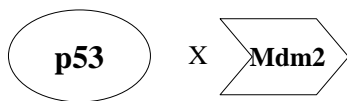
Alterazioni geniche degli attivatori del ciclo cellulare nei tumori umani

Gene	Tipo di alterazione	Tumori umani
ciclina D	amplificazione genica e traslocazione	diversi tipi di tumori
ciclina E	amplificazione genica	tumori dell'ovaio, e della mammella

Ruolo di mdm2 nella regolazione di p53



- Blocca l'attività trascrizionale di p53
- E' una ubiquitino-ligasi che promuove la degradazione di p53
- E' coinvolta nell' export nucleare di p53.

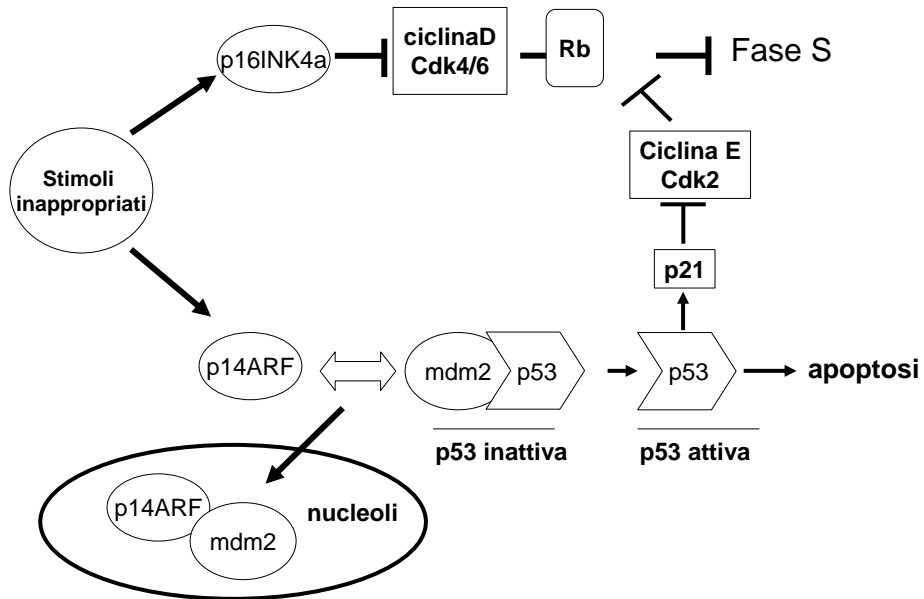


Attivazione ed aumento di p53



Arresto del ciclo cellulare
Apoptosi

p53 in concerto con Rb modula la risposta a stimoli proliferativi inappropriati

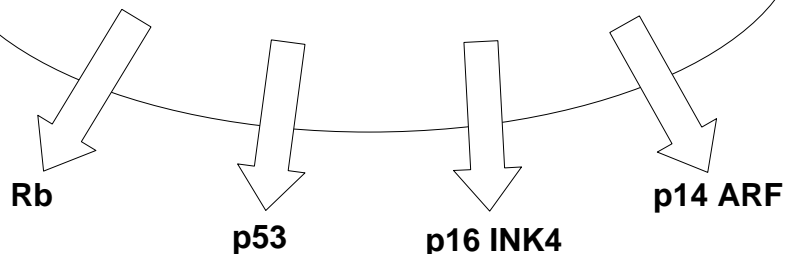


Alterazioni delle 'pathways' di p53 ed Rb nei tumori umani

<u>Gene</u>	<u>Associazione con tumori familiari</u>	<u>Mutazioni spontanee</u>
p53	Sindrome di Li-Fraumeni	piu' del 50% dei tumori
pRb	Retinoblastoma	diversi tumori
INK4a	Melanoma	diversi tumori
p14 ARF	Melanoma	diversi tumori
Mdm2	nr	diversi tumori

Alterazioni del controllo del punto di restrizione

Mutazioni germinali o somatiche di oncosoppressori

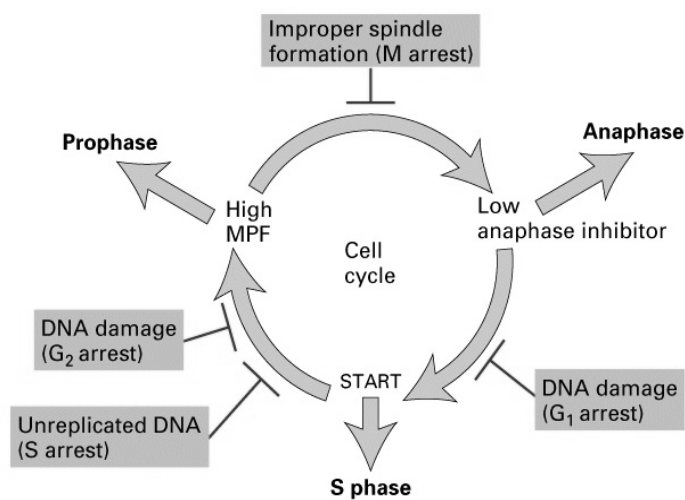


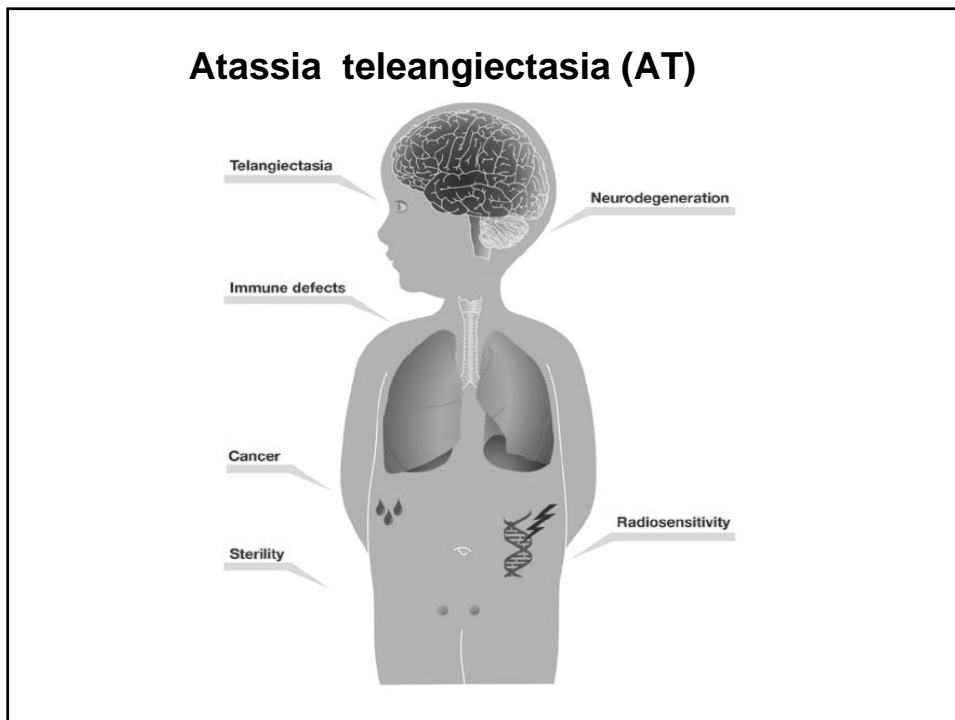
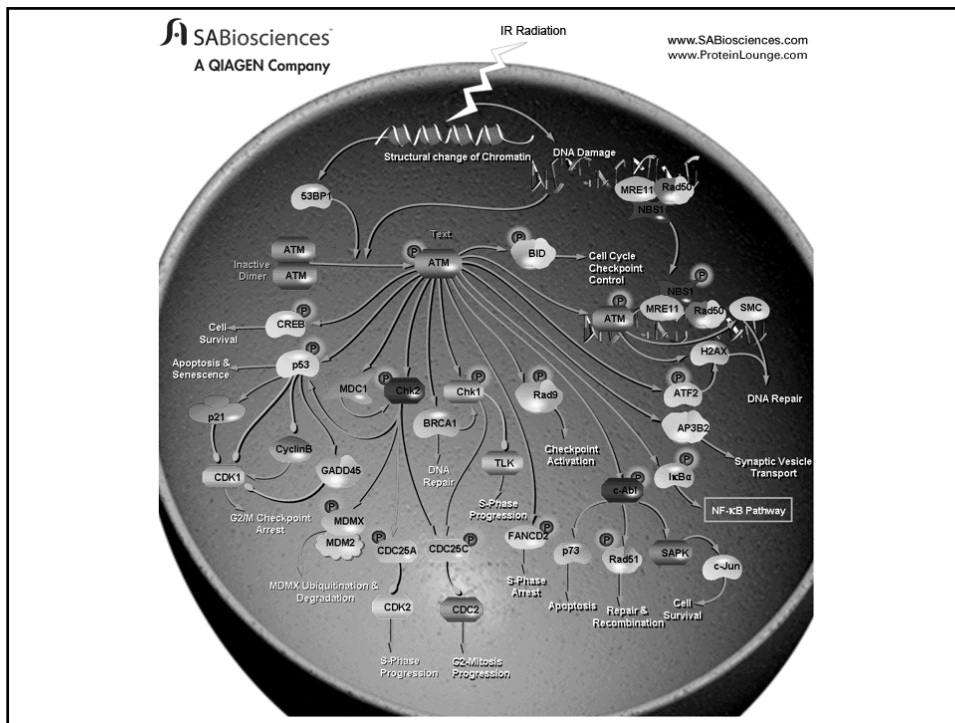
'....the principle task of the cell division cycle is to replicate DNA (without errors during S phase) and to segregate the duplicated chromosomal DNA equally to two daughter cells, during mitosis (or M phase)....'

Charles J. Sherr

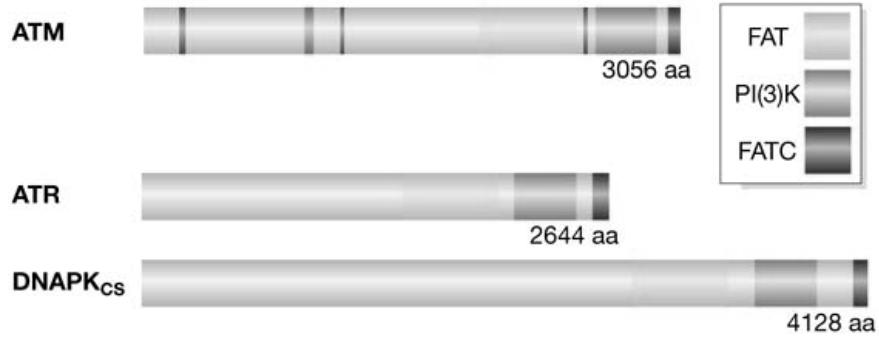
*The Pezcoller Lecture: Cancer Cell Cycle Revisited
[CANCER RESEARCH 60, 2000]*

'Checkpoints' nella regolazione del ciclo cellulare

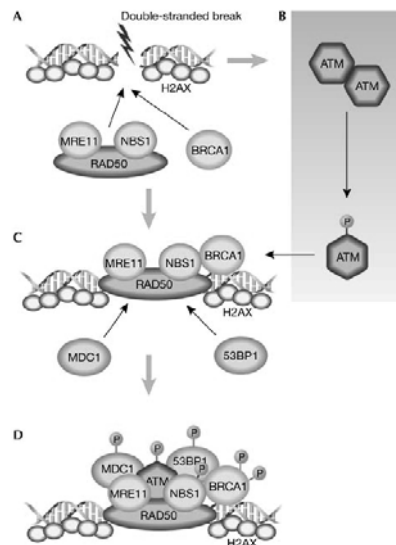




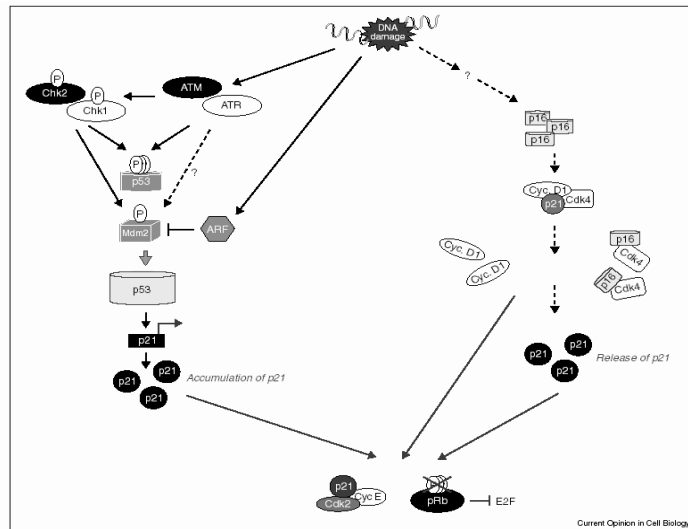
The structure of ATM



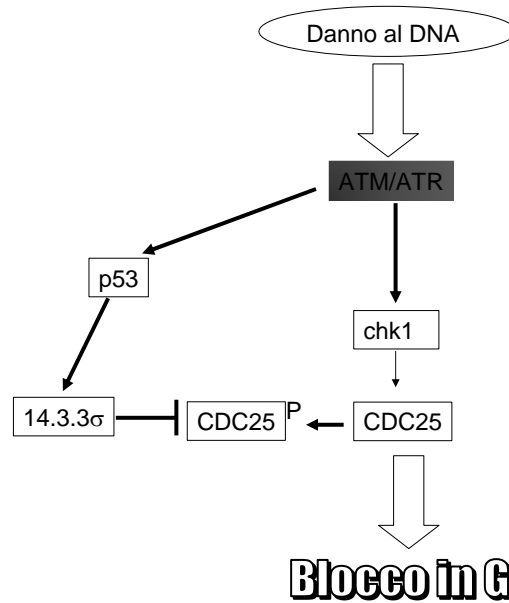
ATM and DNA damage signaling



Regolazione del checkpoint G1/S



Regolazione del 'checkpoint' G2/M



Alterazioni dei 'checkpoints' G1/S e G2/M nei tumori umani

<u>Gene</u>	<u>Associazione con tumori umani familiari</u>	<u>Altri tipi di tumori</u>
CDC25	nr	tumori mammari
ATM	Atassia-Telangiectasia	tumori mammari e linfomi
Chk 2	Sindrome di Li-Fraumeni	nr
p53	Sindrome di Li-Fraumeni	50% dei tumori

Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome?

Li FP and Fraumeni JF

Ann Intern Med. 1969 Oct; 71(4):747-52.

Li-Fraumeni Syndrome is diagnosed if:

- the patient has been diagnosed with a sarcoma at a young age (below 45);
- a first-degree relative has been diagnosed with any cancer at a young age (below 45);
- and another first-degree or a second-degree relative has been diagnosed with any cancer at a young age (below 45) or with a sarcoma at any age.

➤ **Alterazioni del controllo del punto di restrizione**

➤ **Alterazioni dei 'checkpoints' del ciclo cellulare**

