Ionizáló sugárzás hatása a sejtciklusra

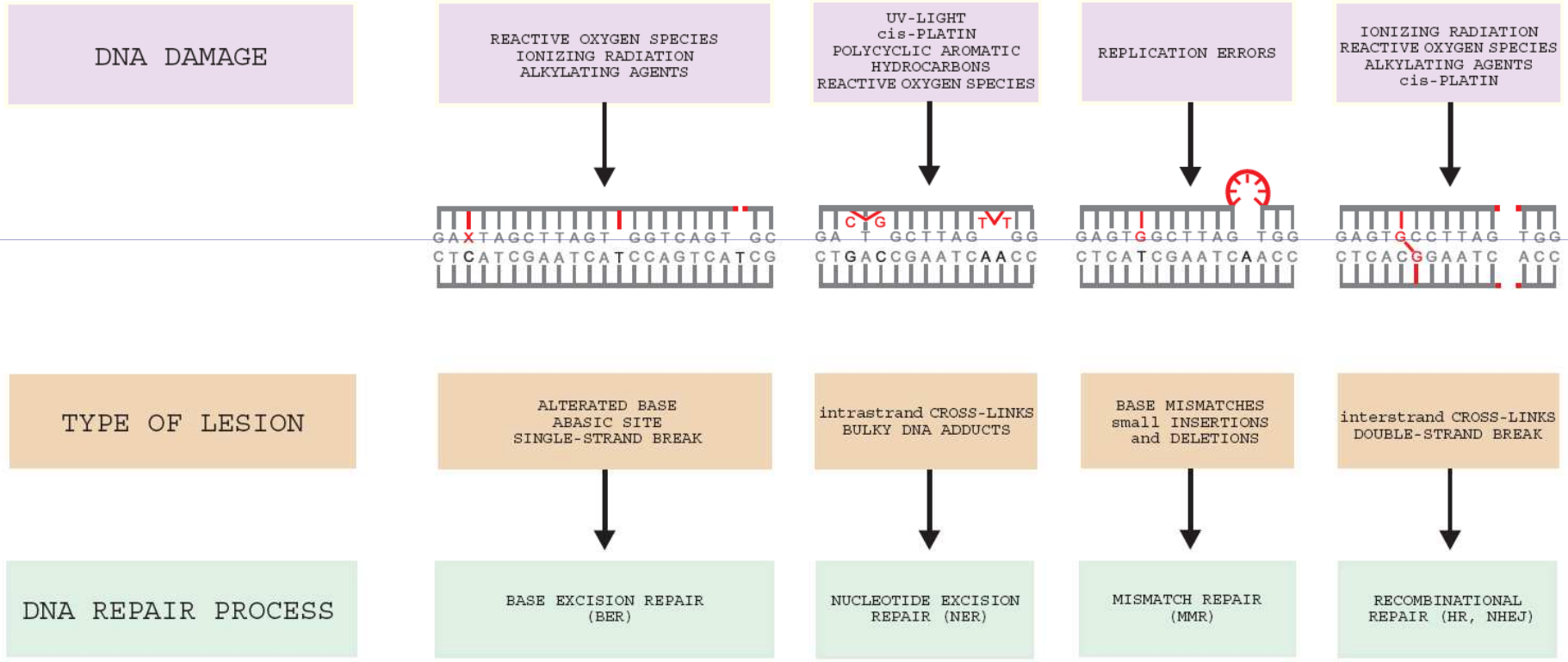


Fig. 1. Summary of the most common types of DNA lesions that can be caused by exogenous or endogenous damaging agents. They may affect a single strand or both strands of the DNA. The assumed repair pathway that operates on the various lesions is also indicated.

A DNS károsodásokat érzékelő rendszer

MRN - MRE11/RAD50/NBS1

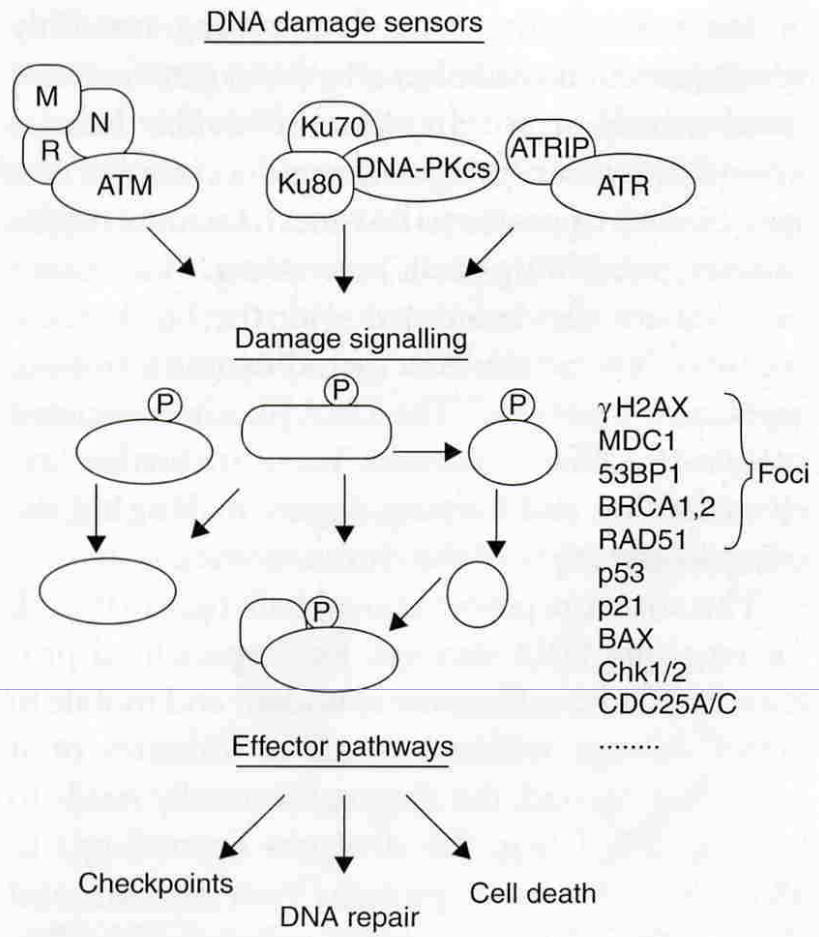


Figure 2.3 The DNA damage response can be divided into sensors and effectors. The sensors consist of protein complexes which recognize DNA damage and include MRN–ATM, Ku–DNA-PKcs, and ATRIP–ATR (see text). These proteins signal to many other proteins which activate three important effector pathways: checkpoints, DNA repair and cell death. Examples of some of the proteins which signal from the sensors to the effector pathways are listed.

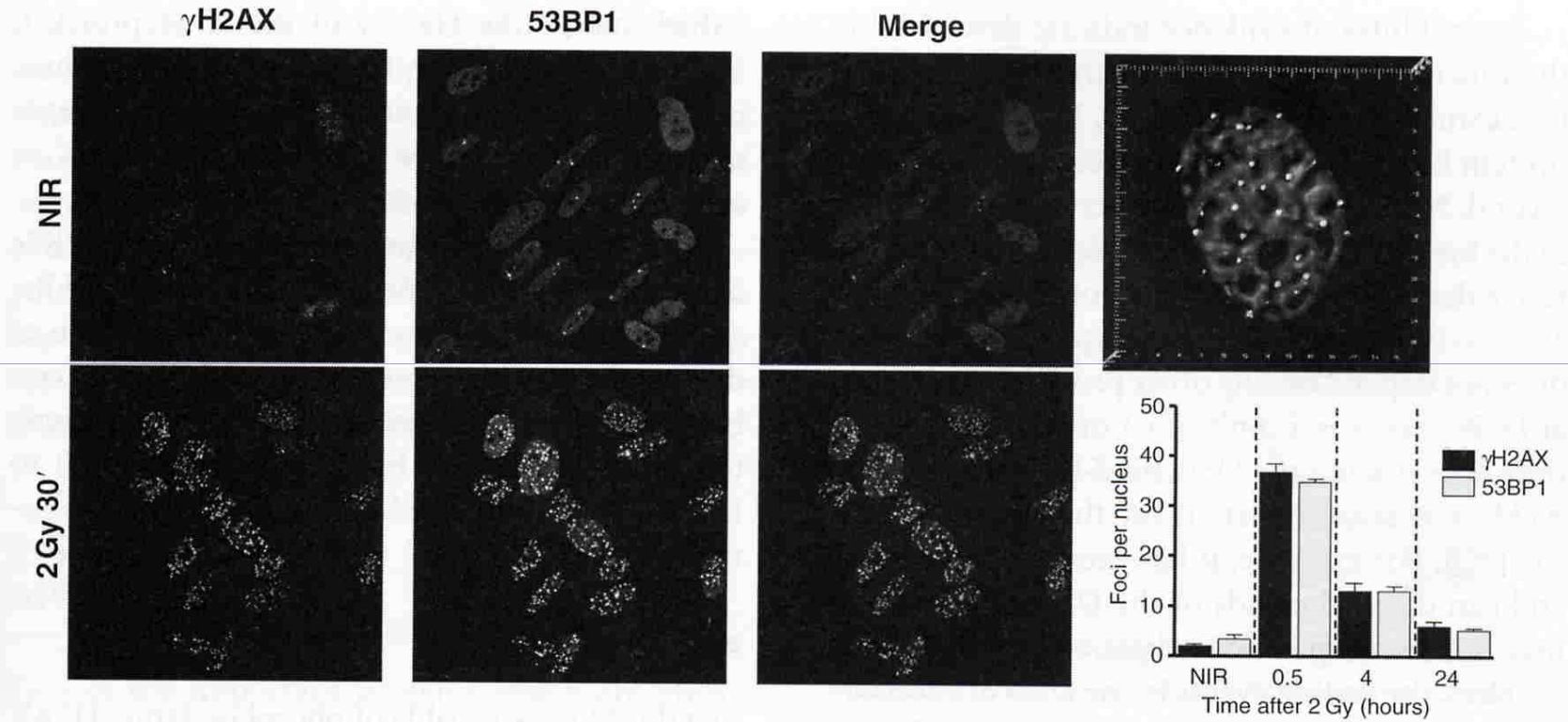
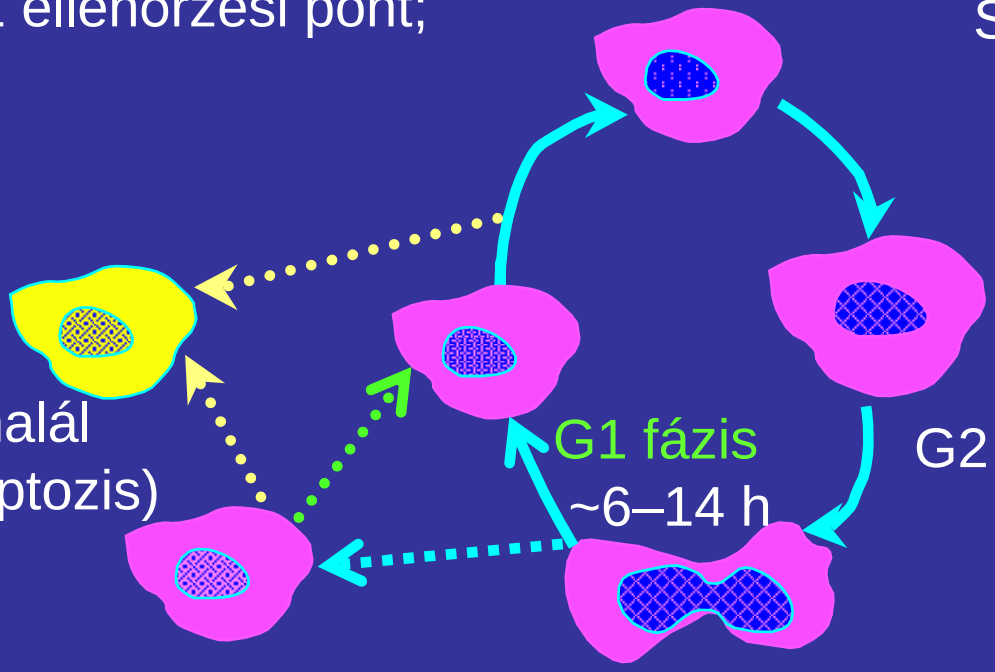


Figure 2.4 Examples of ionizing radiation-induced nuclear foci. Unirradiated and irradiated (2 Gy) cells have been fixed and stained with antibodies that recognize γH2AX and 53BP1, two proteins that interact at sites of DNA damage to form foci after induction of DNA double-strand breaks. These foci form rapidly and then resolve, consistent with the kinetics of DNA double-strand break rejoining. Photographs courtesy of Farid Jallai and Rob Bristow, Princess Margaret Hospital. See colour plate section for full colour images.

Sugárzás és sejtciklus



Go fázis melyből
mitogén stimulusra a
sejt beléphet a sejt ciklusba

- Az ellenőrzési pontok sérülhetnek daganatokban

CDK kinázok és ciklinek

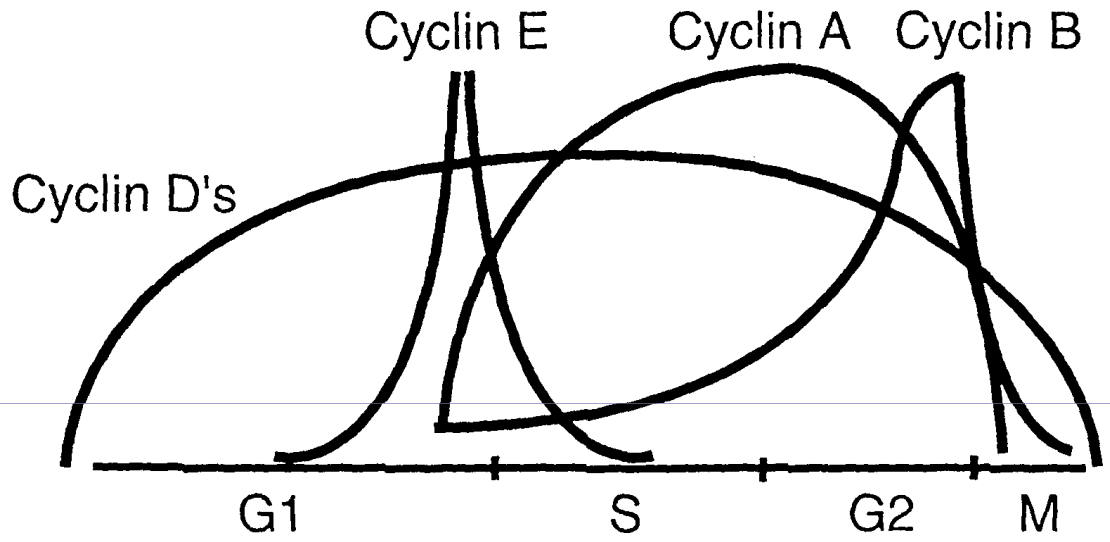
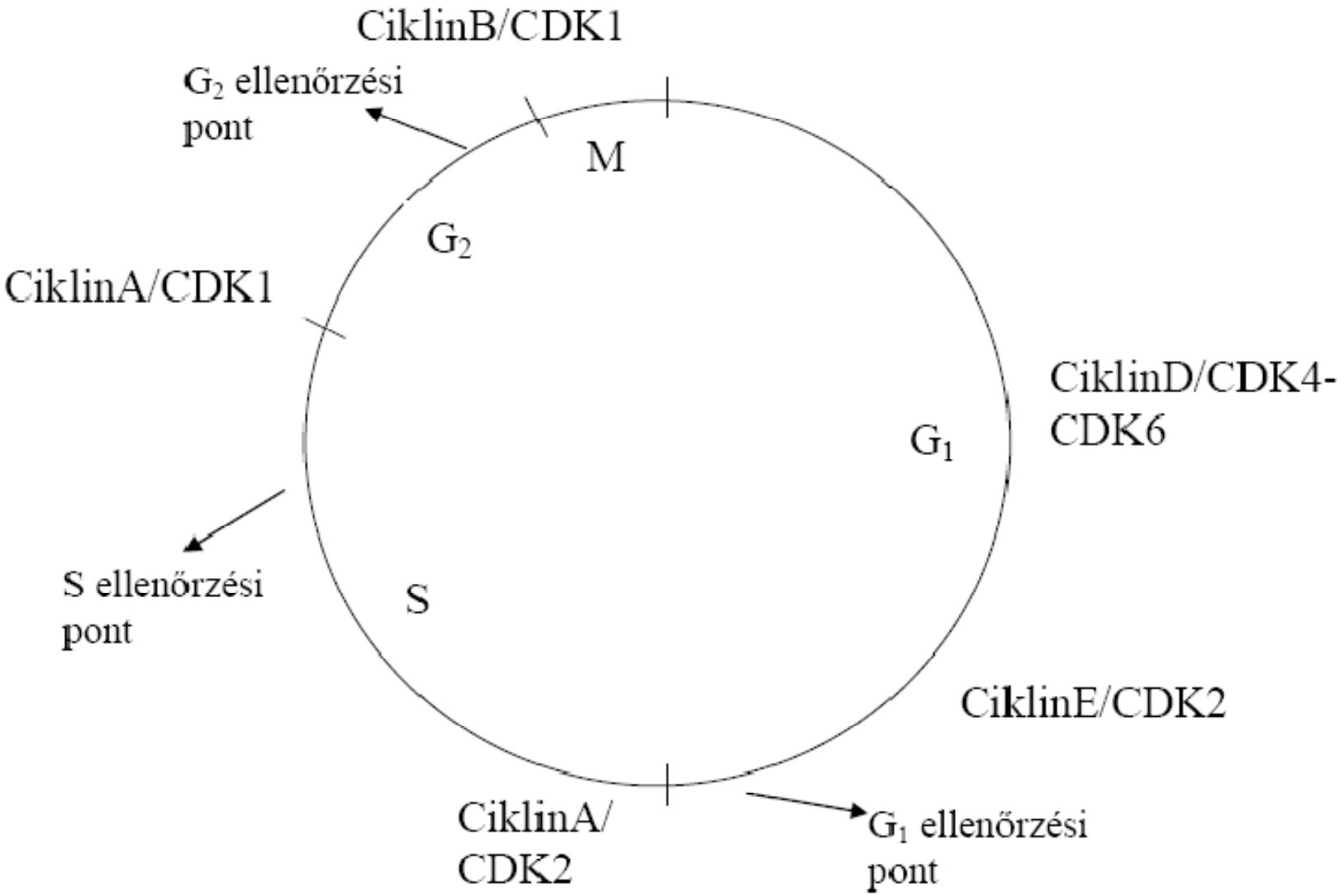


Figure 17.16. Progression through the cell cycle from one phase to the next is governed by protein kinases, activated by cyclins. In mammals, cyclins A through H have been described; each cyclin protein is synthesized at a discrete phase of the cell cycle. Cyclin levels oscillate with phase of cycle, as shown schematically in this figure.

CDK kinázok és ciklinek



Sejthalál és G1 blokk kialakulása

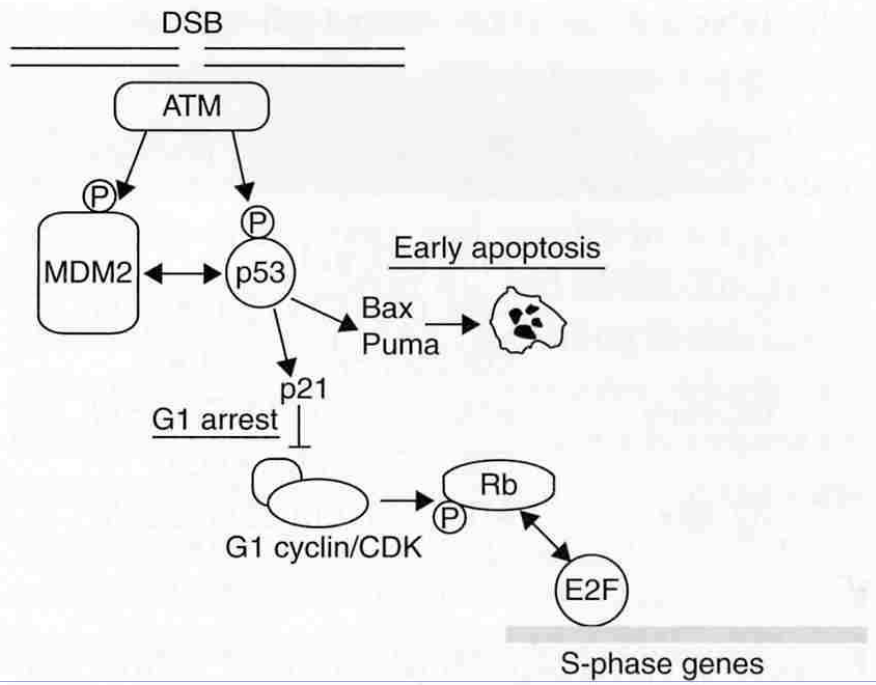
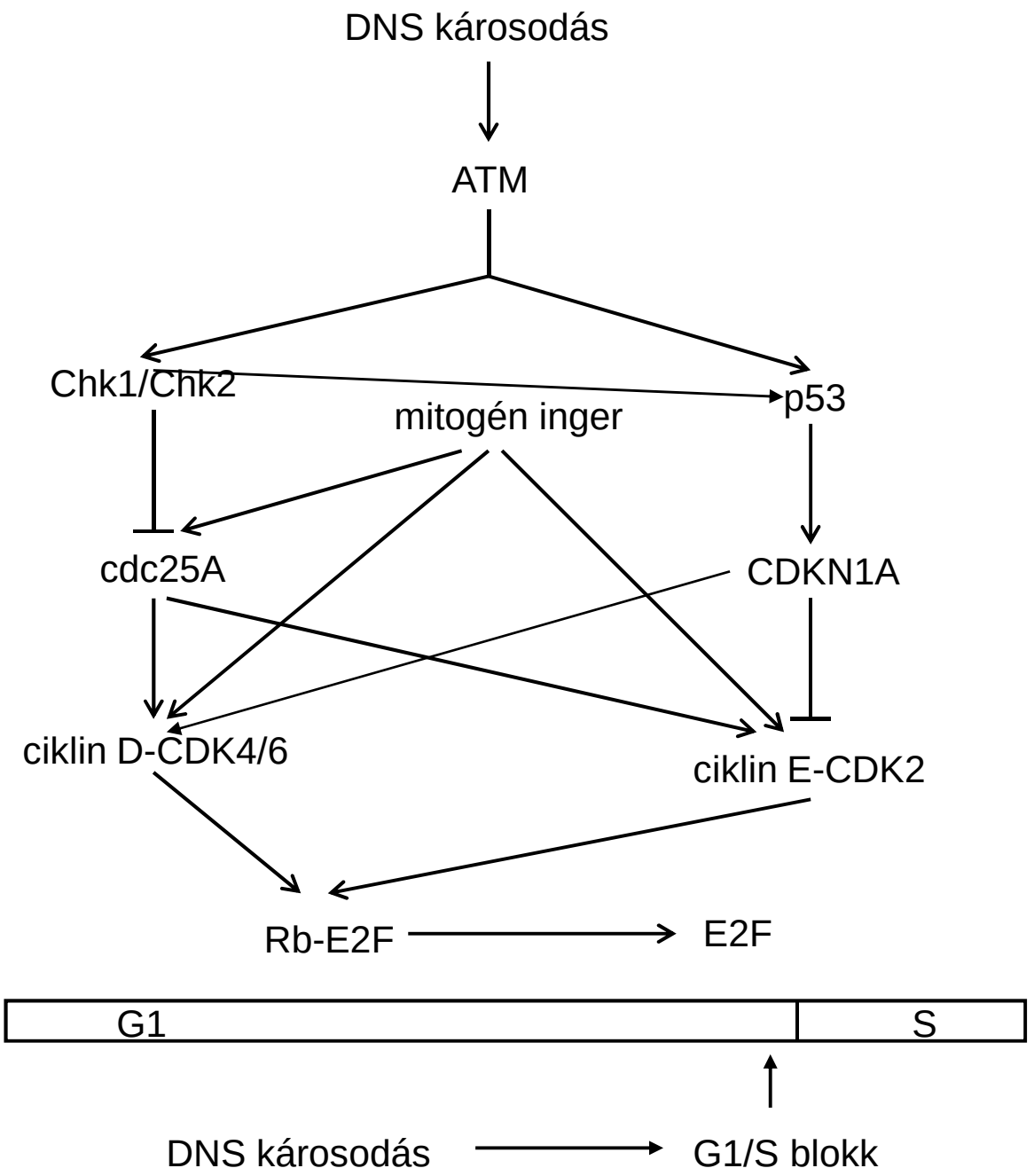


Figure 2.5 Cells irradiated in the G1 phase are influenced by the action of p53. Ataxia telangiectasia mutated (ATM) protein is activated by double-strand DNA breaks (DSBs) and phosphorylates both MDM2 and p53. This leads to stabilization and activation of p53, which then induces genes that can promote apoptosis (Bax, Puma) and induce checkpoints. Induction of p21 inhibits the action of cyclin–cyclin-dependent kinase (CDK) complexes that are necessary for the entry into S phase. Consequently cells are blocked at the G1/S border. In many cancer cells, p53 or other components of this checkpoint are mutated and so it is non-functional.



G1 blokk kialakulás

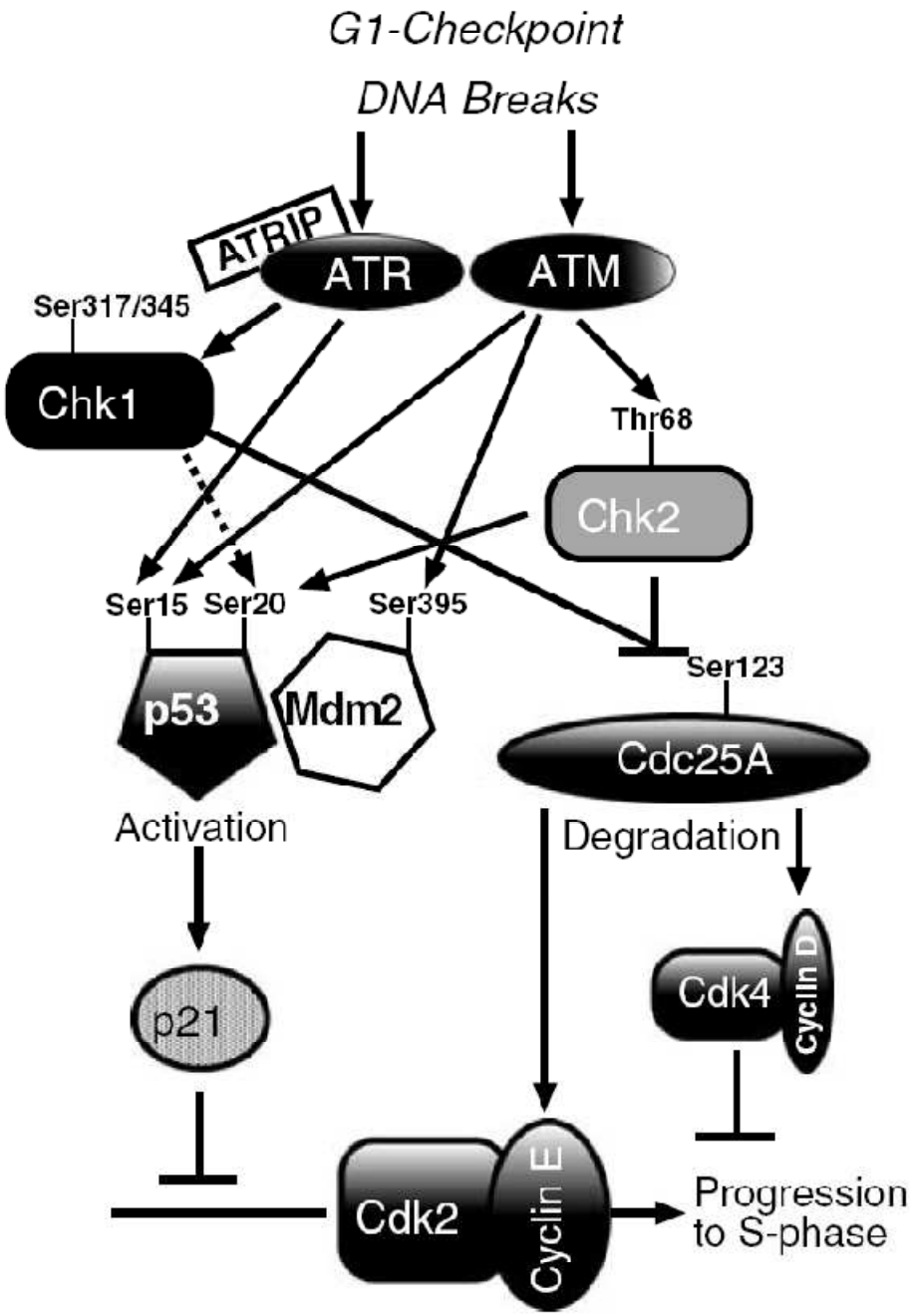


Figure 2 Molecular organization of the G1 checkpoint

Sejtciklus gátlása az S-fázisban

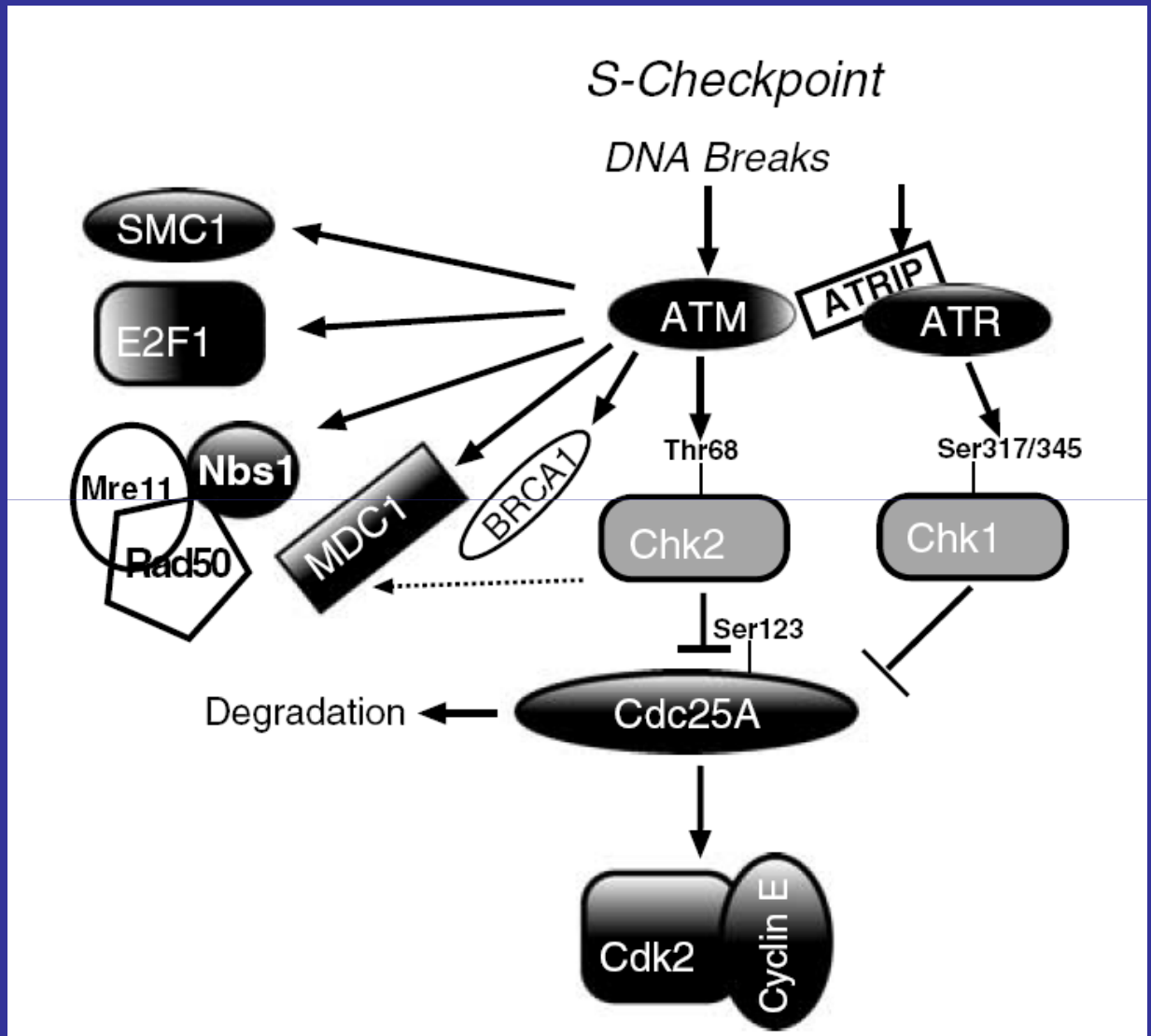
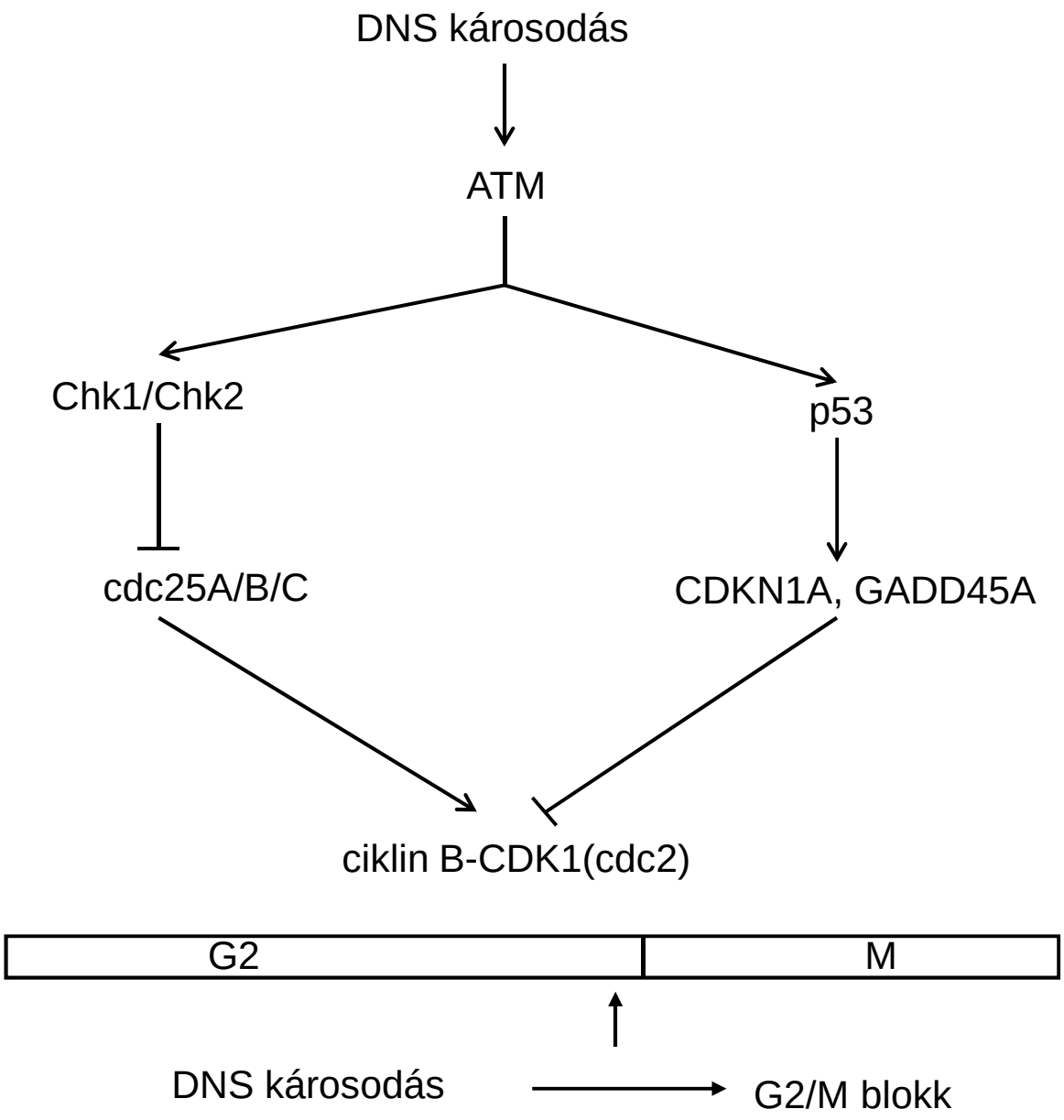


Figure 3 Molecular organization of the S checkpoint



G2 sejtciklus blokk kialakulás

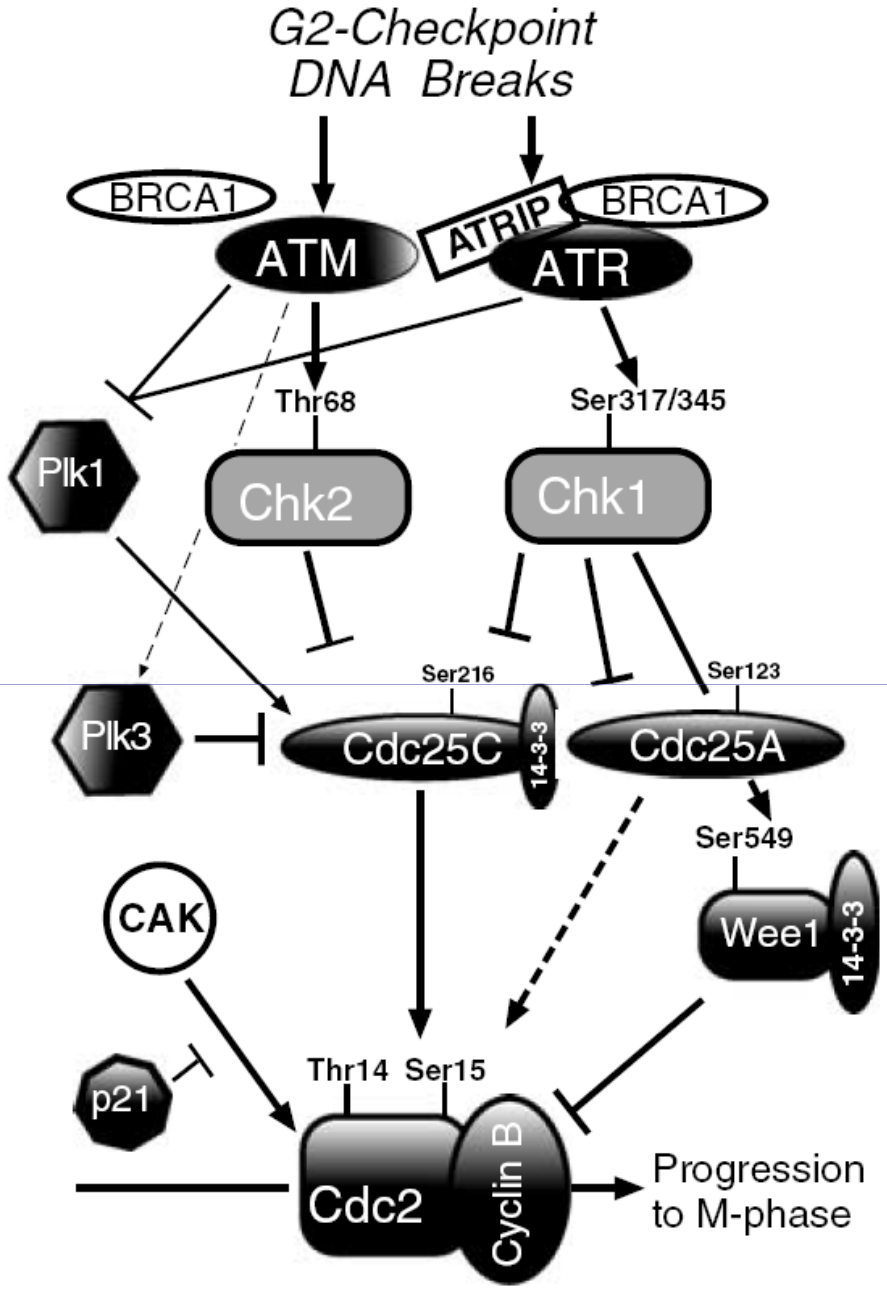
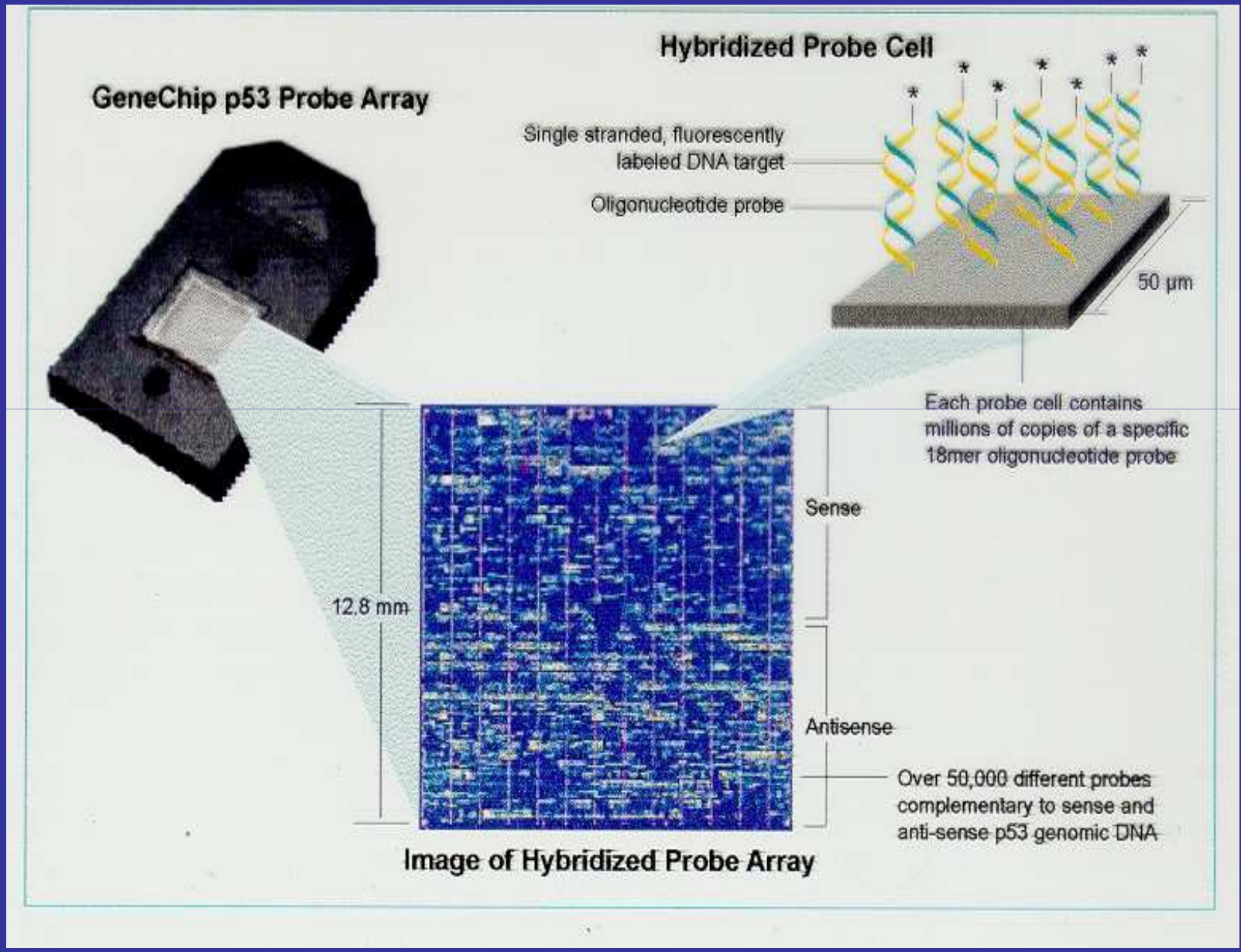


Figure 4 Molecular organization of the G2 checkpoint

Table 2.2 Radiation-induced cell-cycle checkpoints and their characteristics

Position	Primary signalling proteins	Applies to cells irradiated in	Features
G1	ATM, p53, p21	G1	Prevents entry into S
S	ATM, Chk1/Chk12, CDC25A/CDC25C, BRCA1, BRCA2	S	Slows progression through S
G2-early	ATM, Chk1/Chk12, CDC25A/CDC25C, BRCA1, BRCA2	G2	Prevents entry into mitosis
G2-late	ATR, Chk1, CDC25A/CDC25C	All phases	Accumulation of cells in G2

Sugárhatásra kialakuló transzkipció szintű válaszreakciók



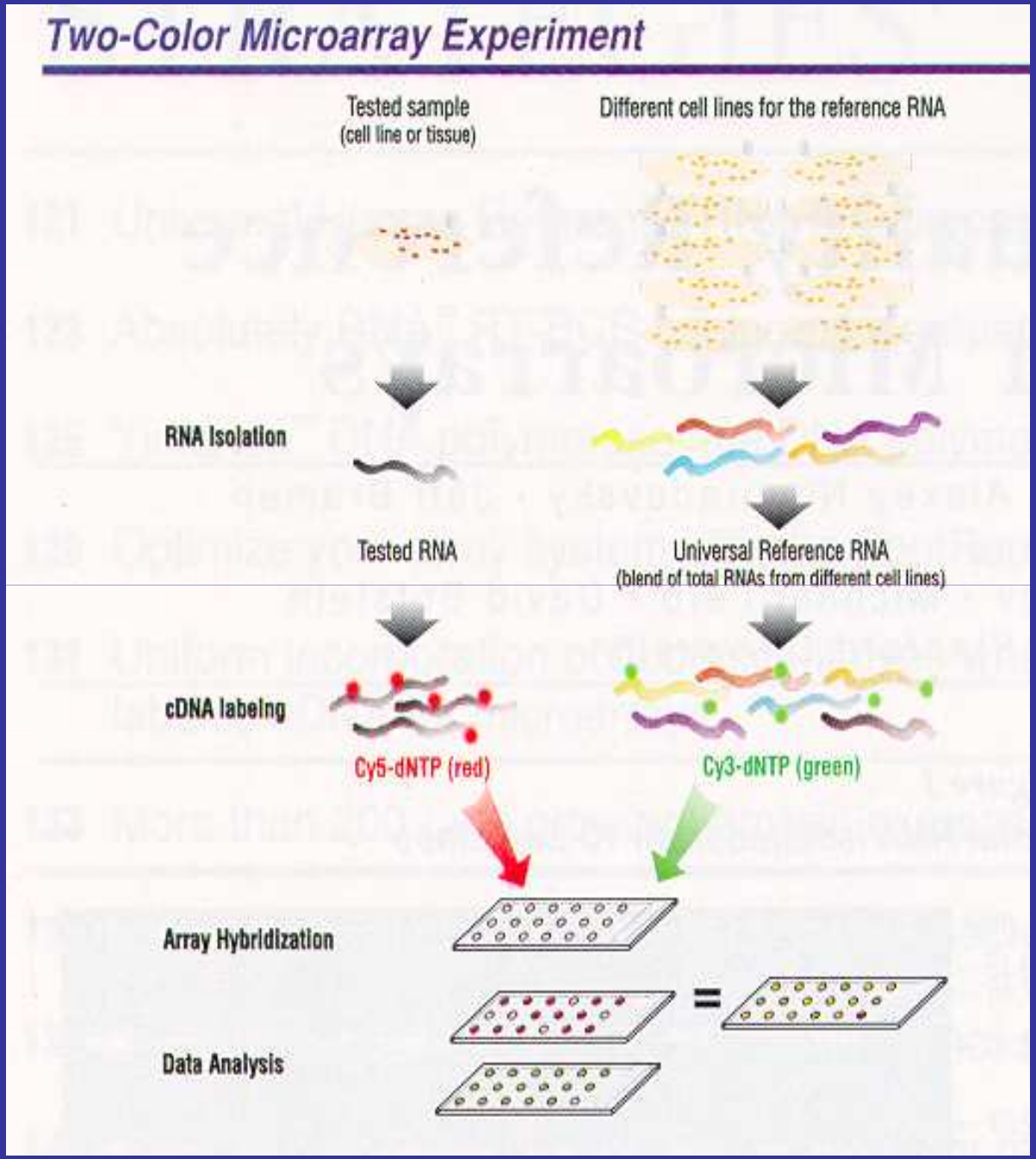
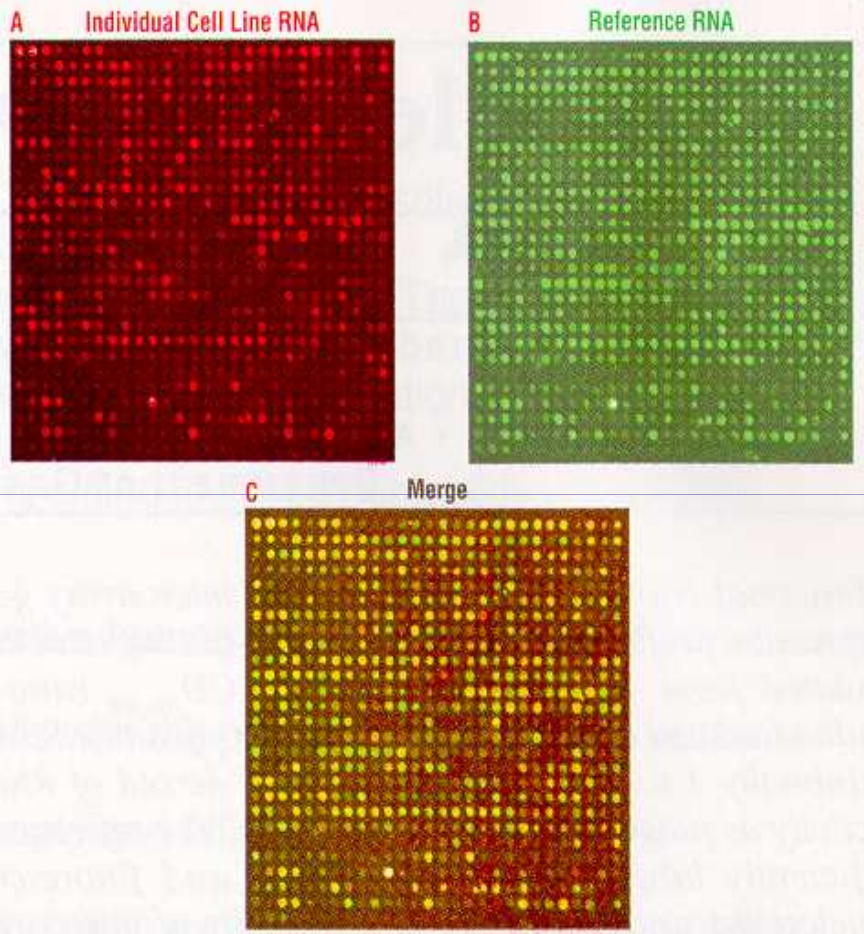

Two-Color Microarray Experiment
Tested sample
(cell line or tissue)
Different cell lines for the reference RNA
RNA Isolation
Tested RNA
Universal Reference RNA
(blend of total RNAs from different cell lines)
cDNA labeling
Cy5-dNTP (red)
Cy3-dNTP (green)
Array Hybridization
Data Analysis

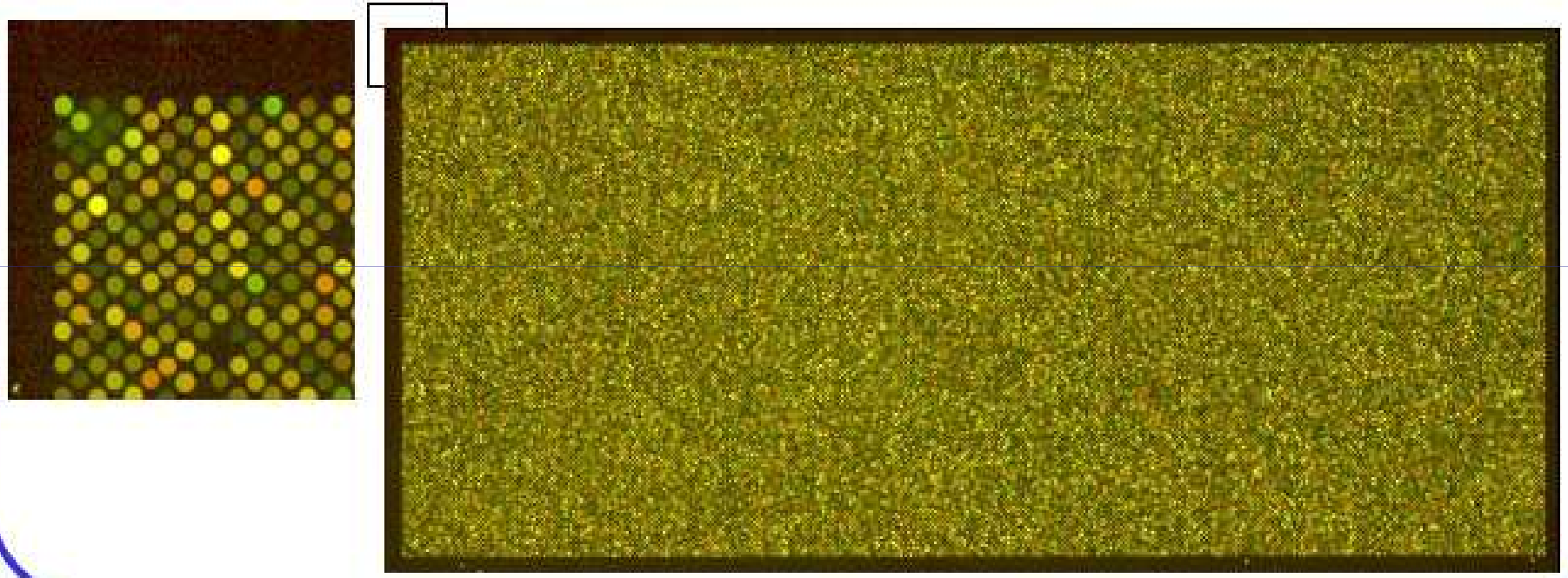
Figure 4

Representative Images from 24,000-Spot Microarray



Cy5-labeled cDNA was reverse transcribed using RNA isolated from a single cell line and Cy3-labeled cDNA using the reference. Both cDNA samples were combined and hybridized to the 24,000-spot human microarray from Stanford University. The microarray was scanned using an Axon scanner and analyzed using GenePix™ Pro 3.0 software. Images represent a portion of the microarray with individual cell line RNA in red (A) and the reference RNA in green (B).

Figure 2. High-Density Human Whole Genome Microarray Image in Log Scale.



Konszenzus sugárválasz gének primer emberi fibroblaszt sejtekben (2 Gy, 2 óra)

(10 gén funkciója nem ismert)

A *p53* útvonal

GADD45A, CDKN1A, PPM1D, BBC3, BTG2, TP53INP1, PCNA

A *CDKN1A* aktiválása sejt-ciklus blokkhoz vezet.

A GADD45A a MAPK jelátviteli folyamatot aktiválja.

A *TP53INP1* befolyásolhatja a *p53* fehérje hatását a *CDKN1A, MDM2 és BAX* promotereken.

A transzkripciós válasz idő- és dózis függése

Válasz DNS károsodásra
- GADD45A
- BTG2
- PCNA
- IER5

Programozott sejt-halál
- BBC3
- TP53INP1

Sejt-ciklus szabályozás
- CDKN1A
- PPM1D
- SERTAD1
- PLK2
- PLK3
- CYR61

Jelátvitel
- NM_153337
- SH2D2A
- GDF15
- THSD1

Fehérje metabolizmus
- AY008274

Energia termelés
- FDXR
- CYP26B1

Sejt kommunikáció
- OR11A1

A sejtek sugárérzékenysége a sejtciklus során

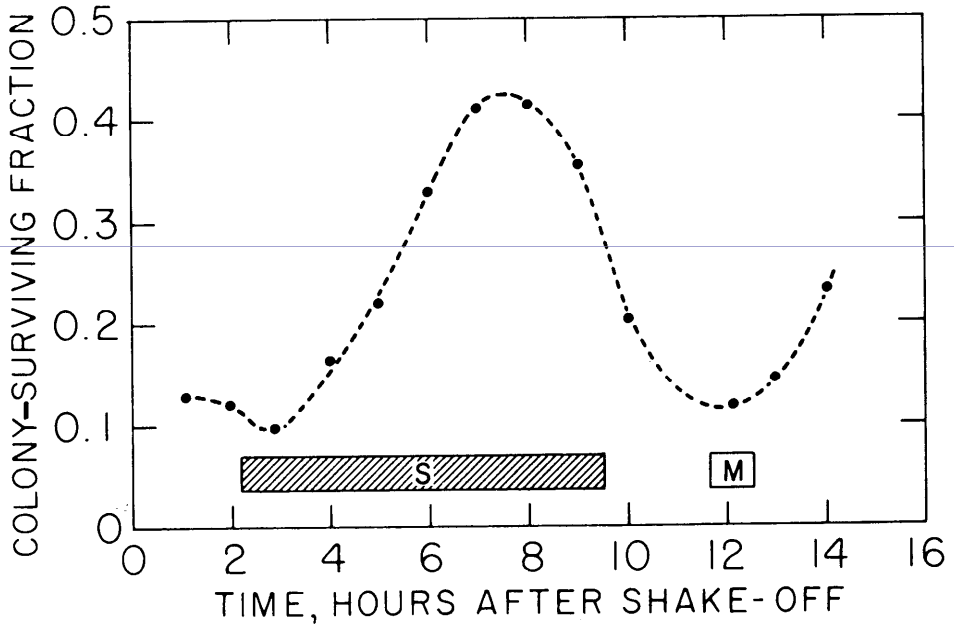


Figure 4.7. Fraction of Chinese hamster cells surviving a dose of 6.6 Gy (660 rad) of x-rays as a function of time. Time zero corresponds to the harvesting of mitotic cells. The cell-surviving fraction increases to a maximum late in S phase. (Adapted from Sinclair WK, Morton RA: X-ray sensitivity during the cell generation cycle of cultured Chinese hamster cells. Radiat Res 29:450–474, 1966, with permission.)

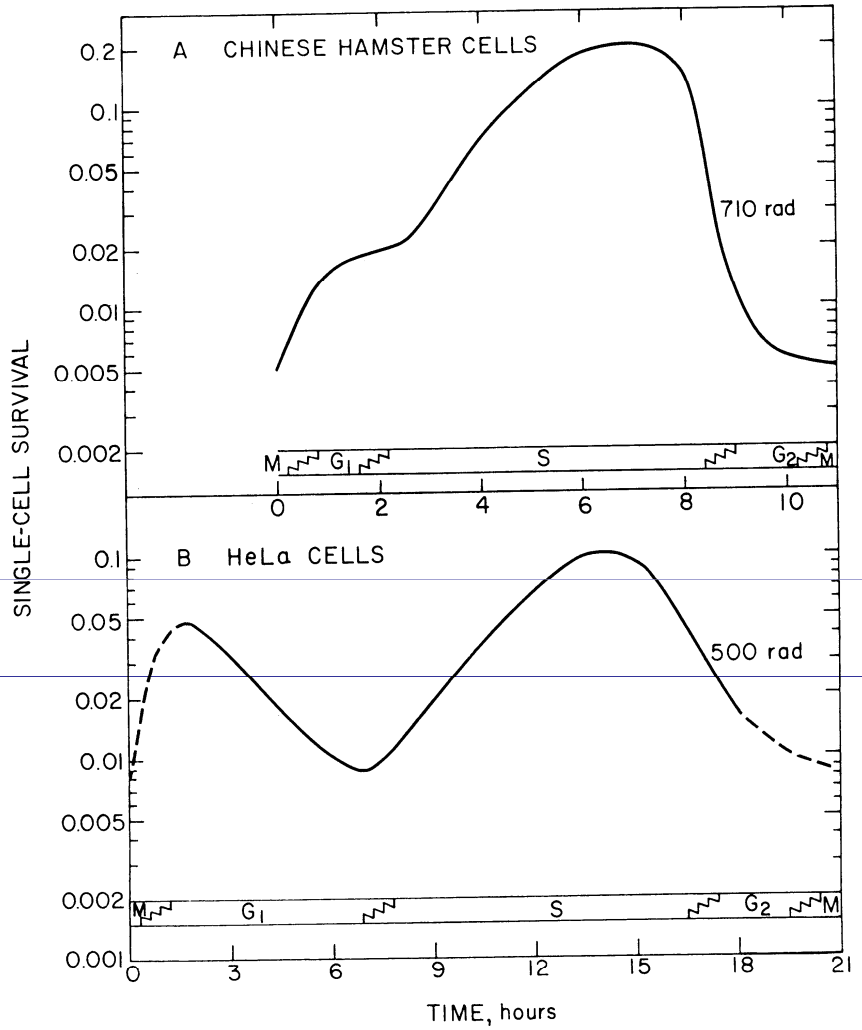
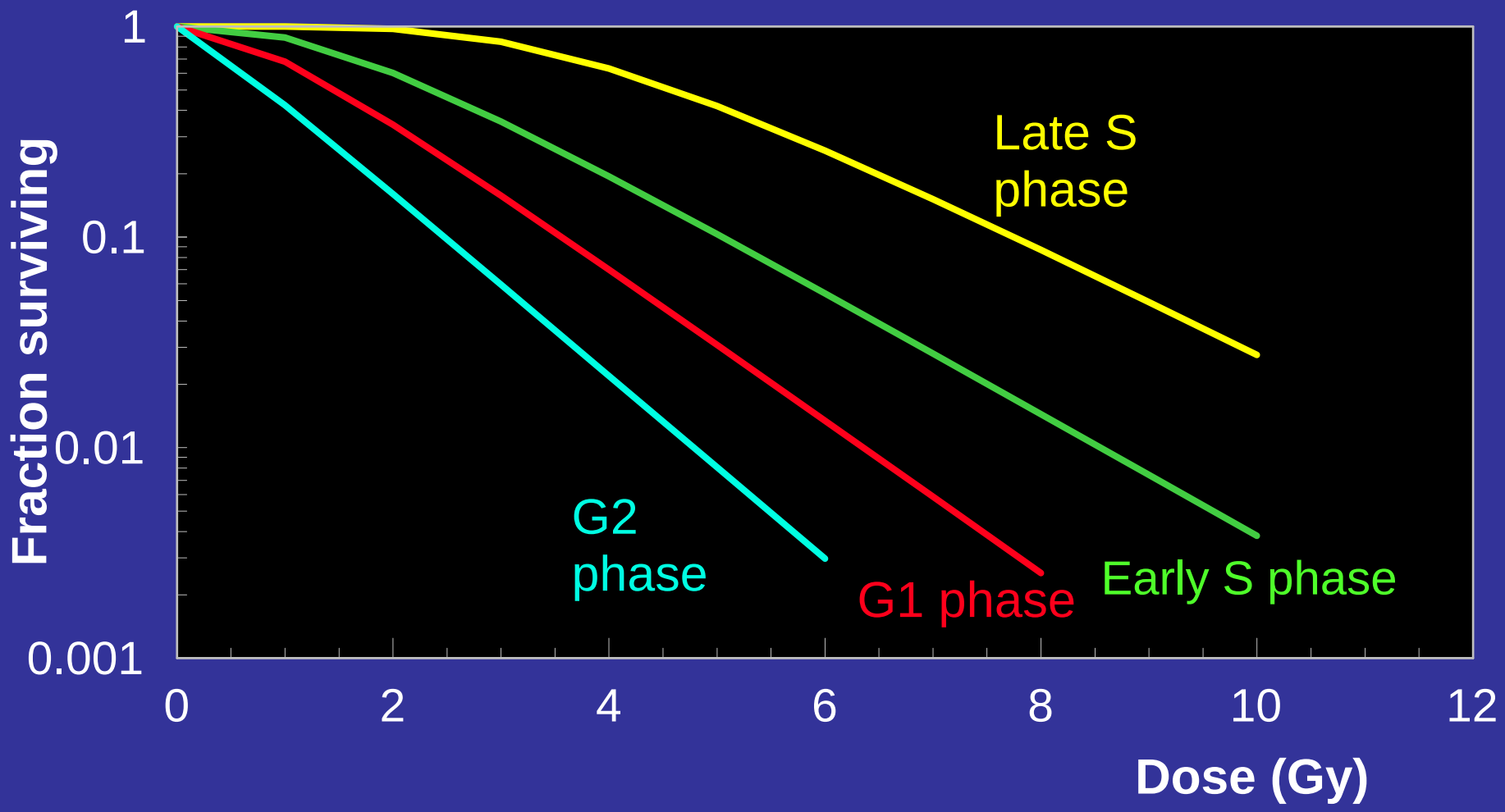


Figure 4.10. Forms of age response for cells with short G_1 phase, represented by hamster cells (**A**), and cells with long G_1 phase, represented by HeLa cells (**B**). The time scales have been adjusted so that S phase has a comparable length on the figure for both cell lines. (From Sinclair WK: Dependence of radiosensitivity upon cell age. In Proceedings of the Carmel Conference on Time and Dose Relationships in Radiation Biology as Applied to Radiotherapy, pp 97–107. BNL Report 50203 (C-57). Upton, NY, 1969, with permission.)

Reproduktiv halál és a sejtciklus



LET hatása a sejtek sugárérzékenységére a sejtciklus egyes fázisaiban

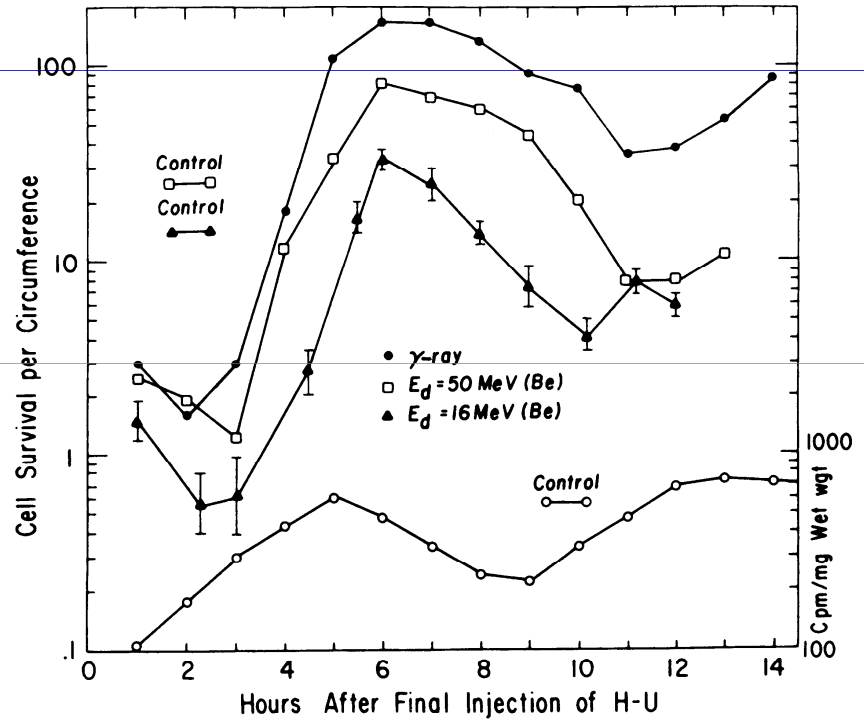


Figure 4.12. The upper three curves represent fluctuations in the survival of jejunal crypt cells exposed to γ-rays or neutrons as they pass through the cell cycle after synchronization with hydroxyurea (H-U). The doses were 11 Gy (1100 rad) of γ-rays; 7 Gy (700 rad) of neutrons generated by 50 MeV $d^+ \rightarrow$ Be; and 6 Gy (600 rad) of neutrons generated by 16 MeV $d^+ \rightarrow$ Be. The lower curve represents the uptake of tritiated thymidine (expressed as counts per minute) per wet weight of jejunum as a function of time after the last injection of hydroxyurea. The first wave indicates crypt stem cells passing through S phase after synchronization at G_1-S phase by hydroxyurea. (From Withers HR, Mason K, Reid BO, et al.: Response of mouse intestine to neutrons and gamma rays in relation to dose fractionation and division cycle. Cancer 34:39–47, 1974, with permission.)

Összefoglalás

- A DNS károsodások szenzor és effektor folyamatokat aktiválnak
- Az effektor folyamatok következménye: sejthalál létrejötte, sejtciklus blokk kialakulása, DNS repair
- A szenzorok közül a legfontosabbak az ATM, az ATR és a DNS-függő protein kináz
- G1, S és G2 sejtciklus blokkot, az adott fázisban bekövetkező DNS sérülések váltanak ki, e blokkok kialakulásában az ATM szerepe alapvető
- Minden sugársérült normál sejtben kialakul egy második G2 blokk, amelyet az ATR aktivál
- A sejtek sugárérzékenysége különböző a sejtciklus egyes fázisaiban
- Nagy LET értékű sugárzások hatását kevésbé befolyásolja a sejtek pozíciója a sejtciklusban