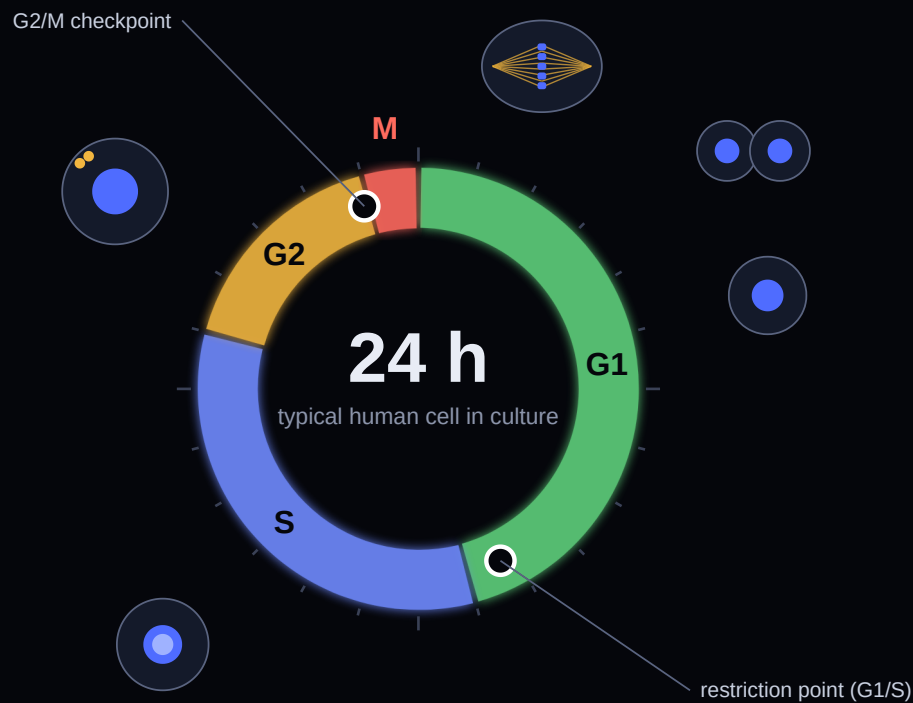




G0: cells can leave G1 and rest outside the cycle

One turn of the cycle for a typical human cell in culture. Timings vary enormously: early frog embryos divide every 30 minutes with almost no G1 or G2, while liver cells may wait a year.

The cell cycle

How a cell grows, copies its DNA and divides in two, and the cyclin-CDK machinery and checkpoints that decide when each step may begin.

■ G1
 ■ S phase and DNA
 ■ G2, spindle and regulators
 ■ M phase

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1. What the cell cycle is

The **cell cycle** is the ordered series of events by which a cell duplicates its contents and divides into two daughter cells. It must achieve two things without error: copy every chromosome exactly once, and give each daughter one complete set.

It has two broad parts:

- **Interphase** (about 95% of the time): **G1** (gap 1), **S** (synthesis of DNA) and **G2** (gap 2).
- **M phase**: **mitosis** (division of the nucleus) and **cytokinesis** (division of the cytoplasm).

The phases of interphase were defined by **Howard and Pelc (1953)**, who fed radioactive thymidine to bean root tips and found by autoradiography that DNA is made only during a limited window, separated from mitosis by two gaps. The molecular controls were discovered by **Leland Hartwell, Tim Hunt and Paul Nurse**, who shared the 2001 Nobel Prize.

Phase	Typical duration*	DNA content	Main events
G1	≈11 h (most variable)	2C	Growth, protein and organelle synthesis; decision to divide
S	≈8 h	2C → 4C	DNA replication; histone synthesis; centrosome duplication
G2	≈4 h	4C	Growth; checks that replication is complete and DNA undamaged; preparation for mitosis
M	≈1 h	4C → 2C	Chromosome segregation and cytokinesis

*For a mammalian cell dividing every 24 hours in culture. "C" is the DNA content of a haploid set; a diploid cell in G1 has 2C.

2. Interphase and G0

G1

After division, a daughter cell grows, makes proteins and organelles, and assesses whether conditions favour another division: are there enough nutrients, growth factors (mitogens), and space? Late in G1 it passes the **restriction point** (called **Start** in yeast), after which it is committed to completing the cycle even if the growth factors are withdrawn. Origins of

replication are "licensed" in G1 by loading the MCM helicase (with ORC, Cdc6 and Cdt1), so that each origin can fire only once in the coming S phase.

S phase

All nuclear DNA is replicated semi-conservatively, from thousands of origins. Histones are made in step so that new DNA is packaged at once. Sister chromatids are held together by **cohesin** rings laid down as the fork passes. The centrosome also duplicates during S phase. High CDK activity blocks re-licensing, which prevents any stretch of DNA being copied twice.

G2

The cell continues to grow and makes proteins needed for mitosis, such as tubulin. It checks that replication is finished and repairs DNA damage before entering M phase.

G0

Cells that stop dividing leave G1 and enter a resting state, **G0**. It may be:

- **Reversible (quiescence):** hepatocytes re-enter the cycle after partial liver removal; resting lymphocytes divide when stimulated by antigen; fibroblasts divide during wound healing.
- **Effectively permanent (terminal differentiation):** most neurons, skeletal muscle fibres and cardiac muscle cells.
- **Senescence:** permanent arrest after telomere shortening or oncogenic stress, maintained by p53-p21 and p16-Rb.

Tissues are often classified as **labile** (continuously dividing: epidermis, gut lining, bone marrow), **stable** (quiescent but able to divide: liver, kidney) and **permanent** (non-dividing: neurons, heart muscle).

3. M phase: mitosis and cytokinesis

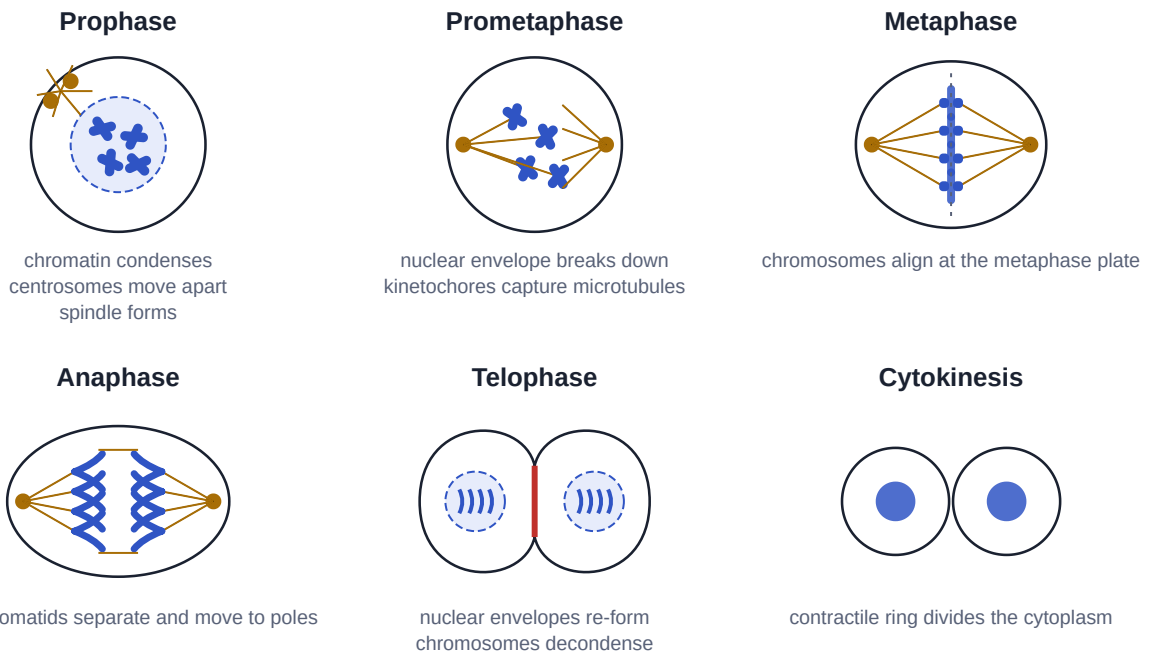


Figure 1. The stages of mitosis in an animal cell. Each chromosome enters mitosis as two sister chromatids joined by cohesin; anaphase begins when that cohesin is cut.

Stage	Key events
Prophase	Chromatin condenses into visible chromosomes (condensin); nucleolus disappears; the two centrosomes move apart and nucleate the mitotic spindle
Prometaphase	CDK1 phosphorylates nuclear lamins and the envelope breaks down; kinetochores form at centromeres and capture spindle microtubules ("search and capture")
Metaphase	Chromosomes align at the equator (metaphase plate), each with sister kinetochores attached to opposite poles (bi-orientation). Best stage for counting chromosomes (karyotyping)
Anaphase	A: separase cuts cohesin; sister chromatids move to opposite poles as kinetochore microtubules shorten. B: poles move apart as polar microtubules slide and elongate
Telophase	Chromosomes reach the poles and decondense; nuclear envelopes re-form around each set; nucleoli reappear

Stage	Key events
Cytokinesis	Animal cells: an actin–myosin II contractile ring forms a cleavage furrow, positioned by the spindle. Plant cells: Golgi vesicles fuse at the phragmoplast to build a cell plate that becomes the new wall

The mnemonic **PPMAT** helps with the order. The result is two genetically identical daughter cells, each with the same chromosome number as the parent.

4. Meiosis

Meiosis produces haploid gametes (or spores) by **one round of DNA replication followed by two divisions**. Meiosis I is **reductional**: homologous chromosomes separate. Meiosis II is **equational**, like mitosis: sister chromatids separate.

Prophase I

Substage	Events
Leptotene	Chromosomes begin to condense as thin threads; programmed double-strand breaks made by Spo11
Zygotene	Homologues pair (synapsis); the synaptonemal complex starts to form
Pachytene	Synapsis complete; paired homologues (bivalents or tetrads); crossing over completed
Diplotene	Synaptonemal complex dissolves; homologues pull apart except at chiasmata . Human oocytes arrest here (dictyotene) from before birth until ovulation
Diakinesis	Maximum condensation; chiasmata move toward chromosome ends (terminalisation); nuclear envelope breaks down

In metaphase I, bivalents align with homologous kinetochores facing opposite poles. In anaphase I, cohesin is removed from chromosome arms but protected at centromeres by **shugoshin**, so homologues separate while sister chromatids stay together until anaphase II.

Feature	Mitosis	Meiosis
Occurs in	Somatic cells	Germ cells (gonads)

Feature	Mitosis	Meiosis
Divisions	One	Two
Daughter cells	Two, diploid (2n)	Four, haploid (n)
Pairing of homologues	No	Yes (synapsis)
Crossing over	Rare	Regular, at least one per bivalent
Genetic make-up	Identical to parent	Different: crossing over and independent assortment
Anaphase	Sister chromatids separate	Homologues (I), then sister chromatids (II)
Role	Growth, repair, asexual reproduction	Sexual reproduction, genetic variation

Non-disjunction, failure of homologues or chromatids to separate, gives aneuploid gametes. Its rate rises steeply with maternal age because oocyte cohesin, loaded before birth, deteriorates over decades; this explains the age-related increase in trisomy 21 (Down syndrome).

5. How the control system was discovered

Experiment	Finding
Cell fusion (Rao and Johnson, 1970)	Fusing an S-phase cell with a G1 cell made the G1 nucleus start replicating early; fusing S with G2 did not make the G2 nucleus replicate again. Fusing a mitotic cell with any interphase cell caused premature chromosome condensation . So there are diffusible activators of S and M phase, and G2 nuclei are blocked from re-replicating
Frog oocytes (Masui and Markert, 1971)	Cytoplasm from mature eggs injected into immature oocytes triggered meiotic maturation. The active factor was named maturation-promoting factor (MPF) , later shown to be CDK1–cyclin B
Yeast <i>cdc</i> mutants (Hartwell, from 1970)	Temperature-sensitive mutants of <i>Saccharomyces cerevisiae</i> arrested at specific stages. <i>CDC28</i> controlled Start. He also introduced the idea of checkpoints

Experiment	Finding
Fission yeast (Nurse, from 1975)	<i>cdc2</i> in <i>Schizosaccharomyces pombe</i> controlled both G1/S and G2/M. In 1987 the human gene (<i>CDK1</i>) rescued yeast <i>cdc2</i> mutants, showing the control system is conserved from yeast to humans
Sea urchin eggs (Hunt, 1983)	A protein was made continuously and destroyed abruptly at each division. He named it cyclin

6. Cyclins and CDKs

The central engine is a family of **cyclin-dependent kinases (CDKs)**. CDKs are present throughout the cycle but are inactive on their own; they switch on only when bound to a **cyclin**. Cyclin levels rise and fall, so CDK activity oscillates. Each cyclin-CDK complex phosphorylates a different set of target proteins, triggering the events of its phase.

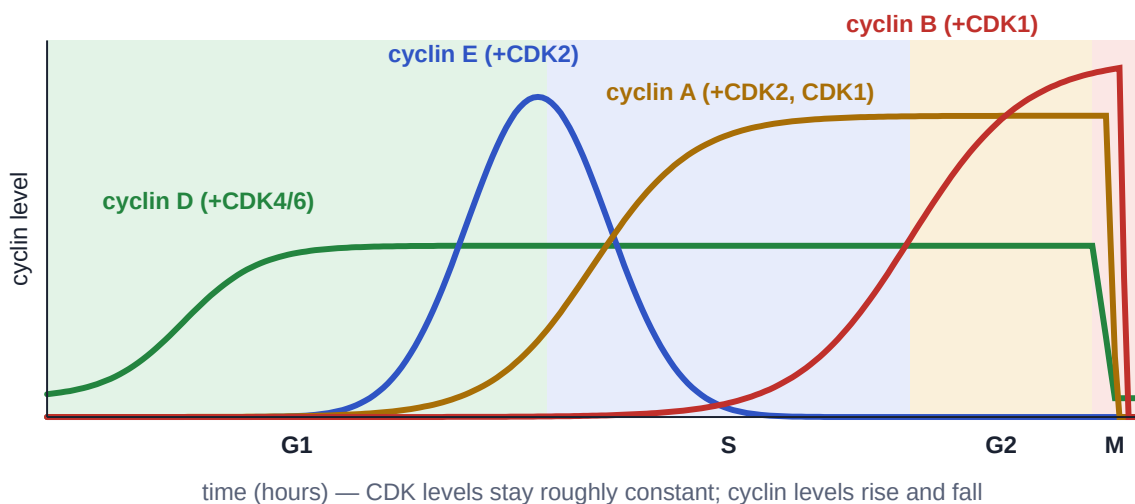


Figure 2. Cyclin levels through the cycle. Cyclins are destroyed by ubiquitin-mediated proteolysis, which makes transitions sharp and irreversible.

Complex	Active in	Main job
Cyclin D–CDK4/6	G1 (made in response to mitogens)	Begins Rb phosphorylation; links growth signals to the cycle
Cyclin E–CDK2	Late G1 → G1/S	Completes Rb phosphorylation; starts DNA replication; centrosome duplication

Complex	Active in	Main job
Cyclin A–CDK2	S phase	Fires origins; blocks re-replication
Cyclin A–CDK1	G2	Prepares for mitosis
Cyclin B–CDK1 (MPF)	G2/M → metaphase	Chromosome condensation, nuclear envelope breakdown, spindle assembly

How CDK activity is controlled

1. **Cyclin binding** partly opens the active site.
2. **Activating phosphorylation** by CDK-activating kinase (**CAK**) on a threonine in the T-loop (Thr161 in CDK1) completes activation.
3. **Inhibitory phosphorylation** by **Wee1** (and Myt1) on Tyr15 (and Thr14) near the ATP site keeps the complex off; the phosphatase **Cdc25** removes it.
4. **CDK inhibitor proteins (CKIs)**: the **INK4** family (p16, p15, p18, p19) blocks CDK4/6; the **Cip/Kip** family (p21, p27, p57) inhibits CDK2 and CDK1 complexes.
5. **Proteolysis**: two ubiquitin ligases destroy cyclins and inhibitors. **SCF** acts at G1/S (destroying p27 and cyclin E); the **anaphase-promoting complex/cyclosome (APC/C)**, with Cdc20 and then Cdh1, destroys securin and cyclin B in mitosis and keeps CDK activity low in G1.

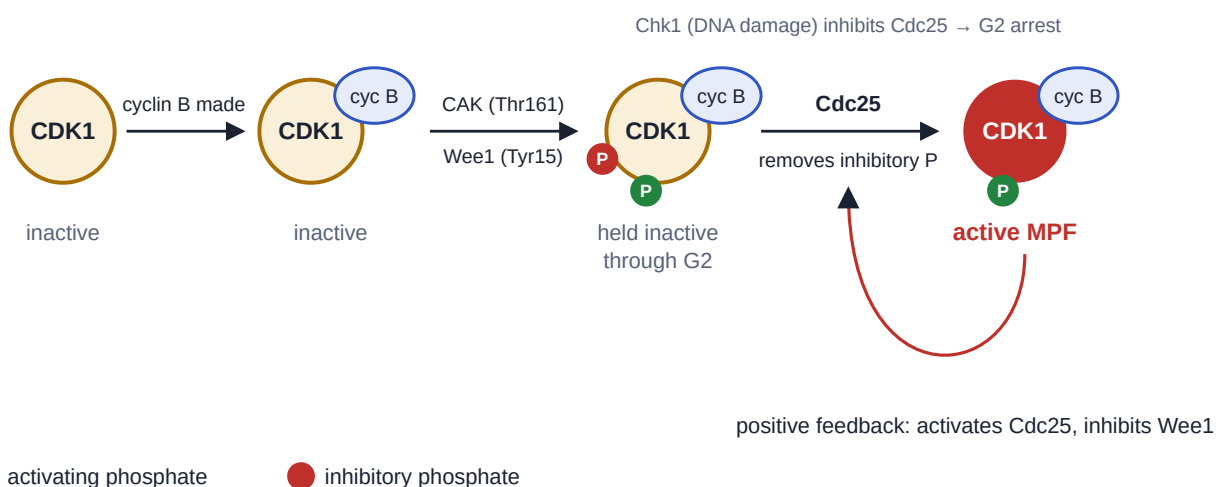
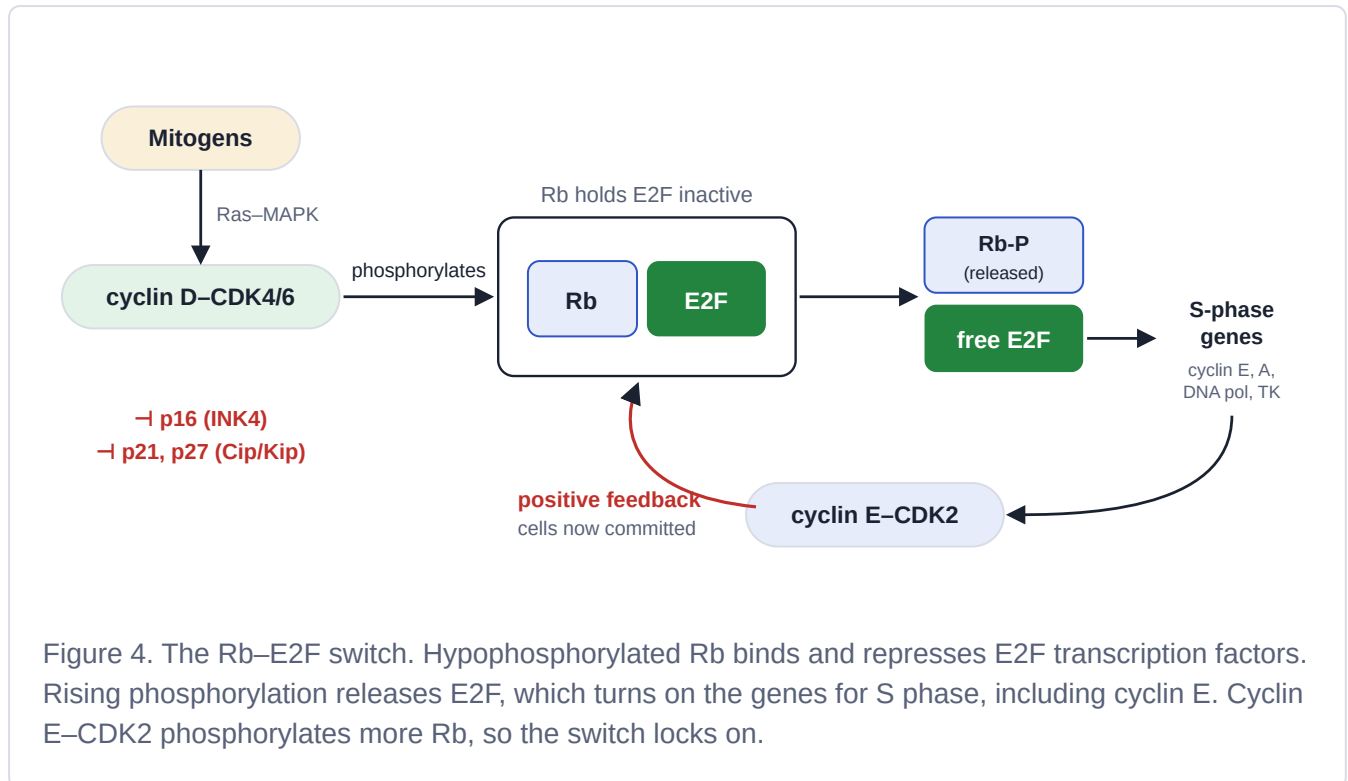


Figure 3. Activation of MPF. Cyclin B–CDK1 builds up in G2 in an inactive, doubly phosphorylated state. When Cdc25 removes the inhibitory phosphate, active CDK1 activates more Cdc25 and inhibits Wee1, so activity rises explosively and the cell enters mitosis all at once.

7. The restriction point: Rb and E2F

Arthur Pardee (1974) found that mammalian cells need growth factors only until a point in late G1; after it, they complete the cycle even if serum is removed. This **restriction point** is controlled mainly by the retinoblastoma protein, **Rb**.



1. Mitogens act through receptor tyrosine kinases and the Ras-MAPK pathway to induce transcription of cyclin D.
2. Cyclin D-CDK4/6 begins to phosphorylate Rb.
3. Partially freed E2F induces cyclin E; cyclin E-CDK2 hyperphosphorylates Rb.
4. Fully released E2F activates S-phase genes (DNA polymerase, thymidine kinase, dihydrofolate reductase, cyclin A). The cell is now committed.

8. Checkpoints

A **checkpoint** is a surveillance mechanism that halts the cycle until a condition is met, so that errors are not passed on. It has three parts: a **sensor** that detects a problem, a **signal transducer**, and an **effector** that stops the cycle machinery.

Checkpoint	Monitors	Mechanism
G1/S (DNA damage)	DNA damage before replication	ATM (double-strand breaks) and ATR (single-stranded DNA) activate Chk2 and Chk1, which stabilise p53 . p53 induces p21 , which inhibits cyclin E–CDK2. Severe damage: p53 induces apoptosis (PUMA, NOXA, BAX)
Intra-S	Stalled forks, damage during replication	ATR–Chk1 slows origin firing; Cdc25A degraded
G2/M	Unreplicated or damaged DNA	Chk1 and Chk2 phosphorylate and inhibit Cdc25 , so CDK1 keeps its inhibitory phosphate; p53–p21 and 14-3-3 σ reinforce the block
Spindle assembly (metaphase/anaphase)	Every kinetochore attached to the spindle and under tension	Unattached kinetochores generate the mitotic checkpoint complex (Mad2, BubR1, Bub3), which inhibits APC/C–Cdc20

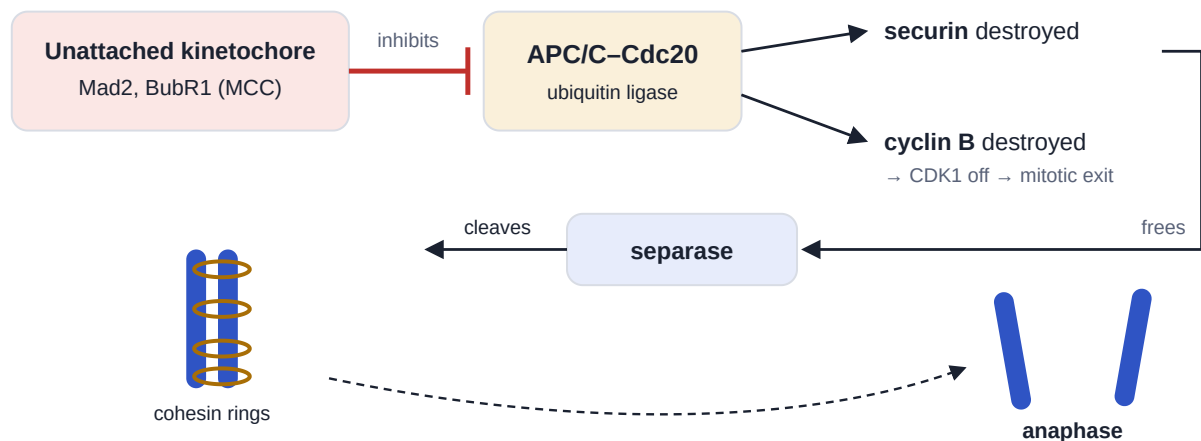


Figure 5. The metaphase-to-anaphase transition. A single unattached kinetochore is enough to hold the whole cell in metaphase. Once all are attached, APC/C ubiquitinates securin, freeing separase to cut cohesin; destruction of cyclin B then lets the cell exit mitosis.

p53, "guardian of the genome"

p53 is normally kept at low levels by **MDM2**, a ubiquitin ligase that marks it for destruction. DNA damage leads ATM/ATR and Chk kinases to phosphorylate p53, blocking MDM2 binding. Stabilised p53 then decides between arrest and repair (p21, GADD45) or apoptosis. *TP53* is mutated in about half of human cancers.

9. Cell cycle and cancer

Cancer is, at heart, a disease of uncontrolled cell division. Almost every tumour has defects in the G1 control pathway, the "p16-cyclin D-CDK4-Rb" axis, or in p53.

Change	Example
Oncogene activation (gain of function)	Cyclin D1 amplification (breast cancer), t(11;14) in mantle cell lymphoma, CDK4 amplification (sarcomas), <i>MYC</i> over-expression
Tumour suppressor loss (two hits)	<i>RB1</i> in retinoblastoma (Knudson's two-hit hypothesis, 1971); <i>CDKN2A</i> (p16) deleted in melanoma and pancreatic cancer; <i>TP53</i> in Li-Fraumeni syndrome
Viral oncoproteins	HPV E7 binds Rb, releasing E2F; HPV E6 targets p53 for degradation (cervical cancer). SV40 large T antigen and adenovirus E1A/E1B act similarly
Checkpoint failure	Weak spindle checkpoint leads to aneuploidy and chromosomal instability

Drugs that act on the cycle

Phase	Drugs	Action
G1	Palbociclib, ribociclib, abemaciclib	CDK4/6 inhibitors; used in hormone-receptor-positive breast cancer
S	Methotrexate, 5-fluorouracil, cytarabine, hydroxyurea	Antimetabolites that starve DNA synthesis
G2	Bleomycin, etoposide	DNA breaks; topoisomerase II inhibition

Phase	Drugs	Action
M	Vincristine, vinblastine, paclitaxel	Disrupt spindle microtubule dynamics
Cycle-non-specific	Alkylating agents (cyclophosphamide), cisplatin	Damage DNA in any phase

Because cycle-specific drugs kill cells only in one phase, they are most effective against rapidly dividing tissues, which also explains their side effects on bone marrow, gut lining and hair follicles.

10. Studying the cell cycle

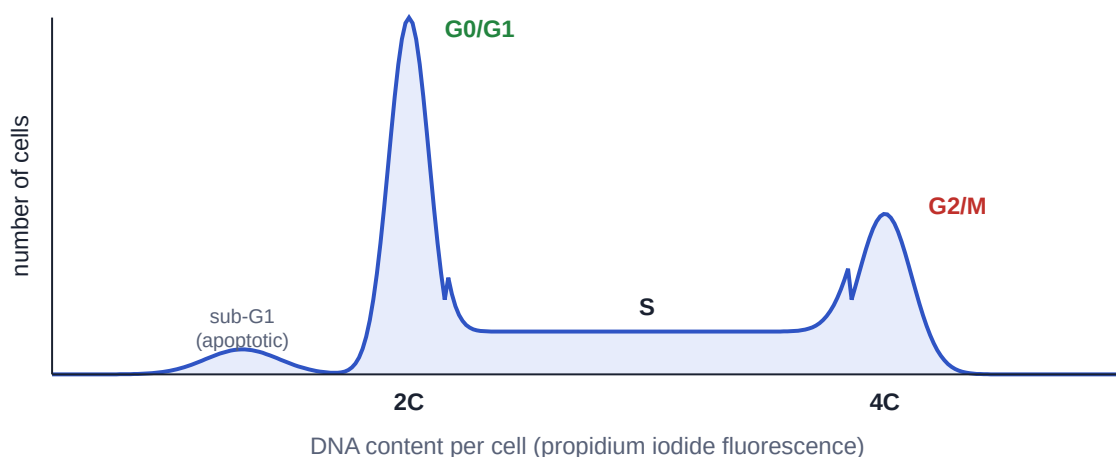


Figure 6. A DNA-content histogram by flow cytometry. Cells are stained with a DNA dye such as propidium iodide; fluorescence is proportional to DNA content. In a typical growing population the G1 peak (2C) is the tallest, the G2/M peak (4C) smaller, and S-phase cells fill the gap between. Apoptotic cells with fragmented DNA fall below 2C (sub-G1).

- **Mitotic index:** the percentage of cells in mitosis in a sample, counted under the microscope.
- **Labelling:** ^3H -thymidine (autoradiography), and now BrdU or EdU, mark cells in S phase.
- **Flow cytometry** of DNA content, often combined with BrdU to separate G1, S and G2/M precisely.
- **Synchronisation:** double thymidine block (arrest at G1/S), nocodazole or colchicine (arrest in mitosis), serum starvation (arrest in G0/G1), mitotic shake-off (loosely attached mitotic cells detach).
- **Live-cell reporters:** the FUCCI system labels G1 nuclei red and S/G2/M nuclei green.

- **Markers:** Ki-67 (all cycling cells, absent in G0), phospho-histone H3 (mitosis), cyclin levels on Western blots.

11. Quick revision

Remember	Fact
Phases	G1 → S → G2 → M (mitosis + cytokinesis); G0 = resting
Discovery of phases	Howard and Pelc, 1953
Nobel 2001	Hartwell (<i>cdc</i> genes, checkpoints), Nurse (<i>cdc2/CDK1</i>), Hunt (cyclins)
MPF	Cyclin B–CDK1; Masui and Markert 1971
CDK regulation	Cyclin binding; CAK activates (Thr161); Wee1 inhibits (Tyr15); Cdc25 removes inhibition; CKIs; SCF and APC/C
CKI families	INK4: p16, p15, p18, p19 (CDK4/6). Cip/Kip: p21, p27, p57
Restriction point	Pardee 1974; Rb phosphorylation frees E2F
Spindle checkpoint	Mad2/BubR1 → APC/C–Cdc20 → securin → separase → cohesin cleaved
DNA damage	ATM/ATR → Chk2/Chk1 → p53 → p21 (G1); Chk1 → Cdc25 (G2)
Meiosis prophase I	Leptotene, zygotene (synapsis), pachytene (crossing over), diplotene (chiasmata), diakinesis

12. End-semester question bank

Long answer (10–15 marks)

1. What is the cell cycle? Describe its phases and the events of each, with a labelled diagram.
2. Describe the stages of mitosis and cytokinesis in animal and plant cells.

3. Describe the stages of meiosis, with special reference to prophase I, and discuss its significance. Compare mitosis and meiosis.
4. Explain the role of cyclins and cyclin-dependent kinases in regulating the cell cycle. How is CDK activity controlled?
5. What are cell cycle checkpoints? Describe the G1/S, G2/M and spindle assembly checkpoints and their molecular basis.
6. Describe the experiments that led to the discovery of MPF, cyclins and *cdc* genes.
7. Explain the role of Rb and p53 in cell cycle control, and how their loss leads to cancer.
8. Discuss how the cell ensures that DNA is replicated only once per cycle and that sister chromatids separate only at anaphase.

Short notes (5 marks)

1. G0 phase
2. Maturation-promoting factor
3. Restriction point
4. Anaphase-promoting complex
5. CDK inhibitors
6. Synaptonemal complex
7. Cohesin and separase
8. p53 as guardian of the genome
9. Cell fusion experiments of Rao and Johnson
10. Flow cytometric analysis of the cell cycle

Differentiate between

1. Mitosis and meiosis
2. Cytokinesis in plant and animal cells
3. Anaphase A and anaphase B
4. G1 and G2 phases
5. INK4 and Cip/Kip inhibitors
6. Quiescence and senescence

Draw and label

1. The cell cycle with checkpoints

2. Stages of mitosis
3. Changes in cyclin levels through the cycle
4. The Rb-E2F pathway
5. A DNA-content flow cytometry histogram

▼ **Very short answer (2 marks), with answers**

1. Longest and most variable phase of the cycle? **G1**
2. DNA content of a diploid cell in G2? **4C**
3. What is MPF? **Cyclin B-CDK1**
4. Kinase that adds the inhibitory phosphate to CDK1? **Wee1**
5. Phosphatase that activates CDK1? **Cdc25**
6. Protein that holds sister chromatids together? **Cohesin**
7. Protease that cleaves cohesin at anaphase? **Separase**
8. Protein that protects centromeric cohesin in meiosis I? **Shugoshin**
9. CDK inhibitor induced by p53? **p21**
10. Transcription factor held inactive by Rb? **E2F**
11. Substage of prophase I in which crossing over occurs? **Pachytene**
12. Stage of mitosis used for karyotyping? **Metaphase**

13. Case-based MCQs

Ten hard questions that test application rather than recall. Choose an answer before opening the explanation.

Q1. A HeLa cell in S phase is fused with a cell in G2. After fusion, the S-phase nucleus continues replicating but the G2 nucleus does not replicate again, even though it is now exposed to S-phase activators. The best explanation is that:

- A. The G2 nucleus has no DNA polymerase
- B. Origins in the G2 nucleus have already fired and cannot be re-licensed while CDK activity is high
- C. S-phase activators cannot enter a G2 nucleus
- D. The G2 nucleus is protected by an intact spindle

▼ **Show answer**

Answer: B. Rao and Johnson's fusion experiments showed a 're-replication block'. Origins are licensed (MCM helicase loaded) only in G1, when CDK activity is low. Once they fire in S phase, high CDK activity prevents new licensing until the cell passes through mitosis. A G2 nucleus has no licensed origins left, so it cannot replicate again.

Q2. Fission yeast carrying a temperature-sensitive *wee1* mutation divide at about half the normal cell size at the restrictive temperature. The most likely explanation is:

- A. CDK1 lacks its activating phosphate, so mitosis is delayed
- B. CDK1 is not held inactive by Tyr15 phosphorylation, so cells enter mitosis before they reach normal size
- C. Cdc25 is destroyed, so cells cannot enter mitosis
- D. Cyclin B is not made

▼ **Show answer**

Answer: B. Wee1 adds the inhibitory phosphate that holds CDK1 off until the cell is large enough. Without Wee1, CDK1 becomes active early and cells divide small. The name *wee* comes from the Scottish word for 'small'; Paul Nurse's discovery of it helped show that CDK1 controls the timing of mitosis.

Q3. A breast cancer patient with an ER-positive tumour starts palbociclib. Tumour cells in which the *RB1* gene has been deleted do not respond. Why?

- A. They lack the oestrogen receptor
- B. Palbociclib acts by preventing CDK4/6 from phosphorylating Rb; without Rb, E2F is already free and the drug target is irrelevant
- C. Rb loss raises cyclin D levels too high for the drug
- D. Rb is needed to take up the drug

▼ Show answer

Answer: B. CDK4/6 inhibitors arrest cells in G1 only by keeping Rb hypophosphorylated so that it continues to repress E2F. If Rb is absent, E2F is constitutively active and blocking CDK4/6 has no effect on S-phase entry. Rb loss is a known mechanism of resistance to these drugs.

Q4. Cells are irradiated during G1. Wild-type cells arrest in G1, but cells lacking functional p53 proceed into S phase with damaged DNA. Which molecule is the direct link between p53 and the G1 arrest?

- A. p16, which inhibits CDK4/6
- B. p21, which inhibits cyclin E-CDK2
- C. MDM2, which degrades cyclin E
- D. Cdc25A, which activates CDK2

▼ Show answer

Answer: B. Damage activates ATM and Chk2, stabilising p53. p53 is a transcription factor whose key G1 target is *CDKN1A*, encoding p21. p21 binds and inhibits cyclin E-CDK2, keeping Rb unphosphorylated. p16 is not induced by p53, and MDM2 degrades p53 itself.

Q5. A drug is found that prevents degradation of securin. Treated cells would be expected to arrest:

- A. In G1, because E2F cannot be released
- B. At metaphase, with aligned chromosomes whose sister chromatids stay joined
- C. In anaphase, with chromatids at the poles
- D. In telophase, unable to re-form the nuclear envelope

▼ **Show answer**

Answer: B. Securin inhibits separase. APC/C-Cdc20 normally ubiquitinates securin at the end of metaphase. If securin cannot be degraded, separase stays inactive, cohesin is not cut and the chromosomes remain at the metaphase plate even if all kinetochores are attached.

Q6. Nocodazole-treated cells arrest in mitosis with chromosomes scattered in the cytoplasm. Which component of the arrest is directly responsible for preventing anaphase?

- A. DNA damage signalling through Chk1
- B. Mad2 and BubR1 at unattached kinetochores inhibiting APC/C-Cdc20
- C. Wee1 phosphorylation of CDK1
- D. Loss of cohesin

▼ **Show answer**

Answer: B. Nocodazole depolymerises microtubules, so kinetochores cannot attach. Unattached kinetochores continuously generate the mitotic checkpoint complex, which blocks APC/C-Cdc20. Securin and cyclin B are therefore not destroyed and the cell stays in mitosis. This is why microtubule drugs are used to collect mitotic cells.

Q7. A 40-year-old woman has a higher risk of a trisomic pregnancy than a 25-year-old. The best cellular explanation involves:

- A. Increased mitotic non-disjunction in the early embryo
- B. Gradual loss of cohesin in oocytes arrested in prophase I for decades, weakening bivalents
- C. Failure of synapsis in zygotene
- D. Loss of shugoshin in meiosis II spermatocytes

▼ Show answer

Answer: B. Human oocytes enter meiosis before birth and arrest in diplotene (dictyotene) until ovulation. Cohesin loaded before birth is barely replenished, so it deteriorates with age. Chiasmata and centromeres lose cohesion, and homologues or sister chromatids separate prematurely at meiosis I or II, producing aneuploid eggs.

Q8. A child develops bilateral retinoblastoma at 8 months. His father had retinoblastoma as a child. According to Knudson's two-hit hypothesis:

- A. Both *RB1* alleles were mutated in the germline
- B. He inherited one mutant *RB1* allele, and a single somatic mutation in any retinal cell inactivates the second
- C. The tumour is caused by a dominant-activating mutation of *RB1*
- D. Both hits must occur in the same cell after birth

▼ Show answer

Answer: B. In the hereditary form every cell already carries one inactive *RB1* allele, so only one more 'hit' in a retinal cell is needed. This explains early onset and multiple, bilateral tumours. In sporadic cases both hits must occur in the same cell, so tumours are usually single and appear later. At the cellular level *RB1* is recessive: both copies must be lost.

Q9. HPV-positive cervical cancer cells are found to have normal *RB1* and *TP53* genes, yet both pathways are inactive. The explanation is that:

- A. HPV E7 binds Rb and releases E2F, while E6 targets p53 for ubiquitin-mediated degradation
- B. HPV integrates into and disrupts both genes
- C. HPV activates CDK4/6 amplification
- D. HPV E6 and E7 are CDK inhibitors

▼ **Show answer**

Answer: A. High-risk HPV oncoproteins inactivate the two major tumour suppressors at the protein level. E7 binds hypophosphorylated Rb and frees E2F, driving S-phase entry; E6 recruits the ubiquitin ligase E6AP to degrade p53, removing the DNA damage checkpoint. The genes themselves need not be mutated.

Q10. In a flow cytometry experiment, cells are treated with a drug and the DNA histogram shows most cells shifting to the 4C peak, with very few at 2C and almost no sub-G1 events. Which drug is most consistent with this profile?

- A. Palbociclib
- B. Hydroxyurea
- C. Nocodazole
- D. Serum starvation

▼ **Show answer**

Answer: C. A pile-up at 4C means arrest in G2 or M. Nocodazole blocks microtubule polymerisation and traps cells in mitosis. Palbociclib and serum starvation arrest cells in G1 (2C); hydroxyurea inhibits ribonucleotide reductase and arrests cells at G1/S or early S. The lack of sub-G1 events shows little apoptosis yet.

For further reading: Alberts, *Molecular Biology of the Cell*; Morgan, *The Cell Cycle: Principles of Control*; Lodish, *Molecular Cell Biology*; Karp, *Cell and Molecular Biology*.