Regulation of Cell Division

Two HeLa cancer cells are just completing cytokinesis. Explain how the cell division of cancer cells like these is misregulated. Identify genetic and other changes that might have caused these cells to escape normal cell cycle regulation.
Coordination of cell division:

- A multicellular organism needs to coordinate cell division across different tissues & organs
  - critical for normal growth, development & maintenance
    - coordinate timing of cell division
    - coordinate rates of cell division
    - not all cells can have the same cell cycle
Frequency of cell division:

- Frequency of cell division varies by cell type
  - **embryo**
    - cell cycle < 20 minute
  - **skin cells**
    - divide frequently throughout life
    - 12-24 hours cycle
  - **liver cells**
    - retain ability to divide, but keep it in reserve
    - divide once every year or two
  - **mature nerve cells & muscle cells**
    - do not divide at all after maturity
    - permanently in G₀
Overview of Cell Cycle Control:

- **Two irreversible points in cell cycle**
  - replication of genetic material
  - separation of sister chromatids

- **Checkpoints**
  - process is assessed & possibly halted

There’s no turning back, now!
Checkpoint control system:

- **Checkpoints**
  - cell cycle controlled by STOP & GO chemical signals at critical points
  - signals indicate if key cellular processes have been completed correctly
Checkpoint control system:

- **3 major checkpoints:**
  - **G₁/S**
    - can DNA synthesis begin?
  - **G₂/M**
    - has DNA synthesis been completed correctly?
    - commitment to mitosis
  - **spindle checkpoint**
    - are all chromosomes attached to spindle?
    - can sister chromatids separate correctly?
G₁/S checkpoint:

- **G₁/S checkpoint** is most critical
  - primary decision point
    - “restriction point”
  - if cell receives “GO” signal, it divides
    - internal signals: cell growth (size), cell nutrition
    - external signals: “growth factors”
  - if cell does **not** receive signal, it exits cycle & switches to **G₀** phase
    - non-dividing, working state
**G₀ phase:**

- **G₀ phase**
  - non-dividing, differentiated state
  - most human cells in G₀ phase

  ![Cell Cycle Diagram]

- **liver cells**
  - in G₀, but can be “called back” to cell cycle by external cues

- **nerve & muscle cells**
  - highly specialized
  - arrested in G₀ & can never divide
Activation of cell division:

- How do cells know when to divide?
  - cell communication **signals**
    - chemical signals in cytoplasm give cue
    - signals usually mean **proteins**
      - activators
      - inhibitors

experimental evidence: Can you explain this?
Molecular signals in the cytoplasm regulate the cell cycle:

**Experiment**

Researchers wondered whether a cell’s progression through the cell cycle is controlled by cytoplasmic molecules. To investigate this, they selected cultured mammalian cells that were at different phases of the cell cycle and induced them to fuse.

**Results**

- **Experiment 1**
  - When a cell in the S phase was fused with a cell in G₁, the G₁ nucleus immediately entered S phase – DNA synthesis

- **Experiment 2**
  - When a cell in the M phase was fused with a cell in G₁, the nucleus immediately began mitosis – a spindle formed and chromosomes condensed, even without duplication

**Conclusion**

Fusing a G₁ cell with a cell in the S or M phase of the cell cycle suggest that molecules present in the cytoplasm during S or M phase control the progression to those phases.
“Go-ahead” signals:

- Protein signals that promote cell growth & division
  - internal signals
    - “promoting factors”
  - external signals
    - “growth factors”

- Primary mechanism of control
  - phosphorylation
    - kinase enzymes
    - either activates or inactivates cell signals
Cell cycle signals:

- **Cell cycle controls**
  - **cyclins**
    - regulatory proteins
    - levels cycle in the cell
  - **Cdks**
    - cyclin-dependent kinases
    - phosphorylates cellular proteins
      - activates or inactivates proteins
  - **Cdk-cyclin complex**
    - triggers passage through different stages of cell cycle

CDK can be compared with an engine and cyclin with a gear box controlling whether the engine will run in the idling state or drive the cell forward in the cell cycle.
Cyclins & Cdk's: 1970s-80s | 2001

- Interaction of Cdk’s & different cyclins triggers the stages of the cell cycle

![Diagram showing the cell cycle stages and MPF activity](image)

- Leland H. Hartwell: checkpoints
- Tim Hunt: Cdk's
- Sir Paul Nurse: cyclins
MPF = Mitosis Promoting Factor
APC = Anaphase Promoting Complex

- Replication completed
- DNA integrity

Chromosomes attached at metaphase plate

G2 / M checkpoint

Spindle checkpoint

G1 / S checkpoint

- Growth factors
- Nutritional state of cell
- Size of cell

Cdk / G2 cyclin (MPF)

Active

Inactive

Inactive

Active

Active

Inactive

Inactive

Spindle checkpoint

Mitosis

Cytokinesis

G2

G1

S

M

C

Chromosomes attached at metaphase plate

G2 / M checkpoint

G1 / S checkpoint

MPF = Mitosis Promoting Factor
APC = Anaphase Promoting Complex
Cyclin & Cyclin-dependent kinases:

- CDKs & cyclin drive cell from one phase to next in cell cycle
  - proper regulation of cell cycle is so key to life that the genes for these regulatory proteins have been highly conserved through evolution
  - the genes are basically the same in yeast, insects, plants & animals (including humans)

CDK and cyclin together form an enzyme that activates other proteins by chemical modification (phosphorylation). The amount of CDK molecules is constant during the cell cycle, but their activities vary because of the regulatory function of the cyclins.
External signals:

- Growth factors
  - coordination between cells
  - protein signals released by body cells that stimulate other cells to divide
    - density-dependent inhibition
      - crowded cells stop dividing
      - each cell binds a bit of growth factor
        - not enough activator left to trigger division in any one cell
    - anchorage dependence
      - to divide cells must be attached to a substrate
        - “touch sensor” receptors
Growth factor signals:

growth factor

cell surface receptor

protein kinase cascade

cyttoplasm

nuclear membrane

nuclear pore

cell division

chromosome

Cdk

e2F
Rb

P
Example of a Growth Factor:

- **Platelet Derived Growth Factor (PDGF)**
  - made by platelets in blood clots
  - binding of PDGF to cell receptors stimulates cell division in connective tissue
  - heal wounds

Don't forget to mention erythropoietin! (EPO)
Growth Factors and Cancer:

- Growth factors can create cancers
  - **proto-oncogenes**
    - normally activates cell division
      - growth factor genes
      - become oncogenes (cancer-causing) when mutated
        - if switched “ON” can cause cancer
        - example: RAS (activates cyclins)
  - **tumor-suppressor genes**
    - normally inhibits cell division
    - if switched “OFF” can cause cancer
    - example: p53
Cancer & Cell Growth:

- Cancer is essentially a failure of cell division control
  - unrestrained, uncontrolled cell growth
- What control is lost?
  - lose checkpoint stops
  - gene **p53** plays a key role in G$_1$/S restriction point
    - p53 protein halts cell division if it detects damaged DNA
      - options:
        - stimulates repair enzymes to fix DNA
        - forces cell into G$_0$ resting stage
        - keeps cell in G$_1$ arrest
        - causes apoptosis of damaged cell
  - **ALL** cancers have to shut down p53 activity

**p53** is the **Cell Cycle Enforcer**

p53 discovered at Stony Brook by Dr. Arnold Levine
### DNA Damage and p53

#### Step 1
DNA damage is caused by heat, radiation, or chemicals.

#### Step 2
Cell division stops, and p53 triggers enzymes to repair damaged region.

#### Step 3
p53 triggers the destruction of cells damaged beyond repair.

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#### Abnormal p53

#### Step 1
DNA damage is caused by heat, radiation, or chemicals.

#### Step 2
The p53 protein fails to stop cell division and repair DNA. Cell divides without repair to damaged DNA.

#### Step 3
Damaged cells continue to divide. If other damage accumulates, the cell can turn cancerous.
Development of Cancer:

- Cancer develops only after a cell experiences ~6 key mutations ("hits")
  - **unlimited growth**
    - turn **on** growth promoter genes
  - **ignore checkpoints**
    - turn **off** tumor suppressor genes (p53)
  - **escape apoptosis**
    - turn **off** suicide genes
  - **immortality = unlimited divisions**
    - turn **on** chromosome maintenance genes
  - **promotes blood vessel growth**
    - turn **on** blood vessel growth genes
  - **overcome anchor & density dependence**
    - turn **off** touch-sensor gene
What causes these “hits”?  

- Mutations in cells can be triggered by:
  - UV radiation
  - chemical exposure
  - radiation exposure
  - heat
  - cigarette smoke
  - pollution
  - age
  - genetics

1. A tumor grows from a single cancer cell.
2. Cancer cells invade neighboring tissue.
3. Cancer cells spread through lymph and blood vessels to other parts of the body.
Tumors:

- Mass of abnormal cells
  - **Benign tumor**
    - abnormal cells remain at original site as a lump
      - p53 has halted cell divisions
      - most do not cause serious problems & can be removed by surgery
  - **Malignant tumor**
    - cells leave original site
      - lose attachment to nearby cells
      - carried by blood & lymph system to other tissues
      - start more tumors = metastasis
    - impair functions of organs throughout body

13 lb. fatty tumor
Traditional treatments for cancers:

- Treatments target rapidly dividing cells
  - high-energy radiation
    - kills rapidly dividing cells
  - chemotherapy
    - stop DNA replication
    - stop mitosis & cytokinesis
    - stop blood vessel growth
New “miracle drugs”

- Drugs targeting proteins (enzymes) found only in cancer cells
  - **Gleevec**
    - treatment for adult leukemia (CML) & stomach cancer (GIST)
    - 1st successful drug targeting only cancer cells

![Gleevec: HOW IT WORKS](image)

**Novartes**
Recent advances in understanding the cell cycle and cell cycle signaling have led to advances in cancer treatment. Coupled with the ability to sequence the DNA of cells in a particular tumor, treatments are becoming more “personalized”.

Precision medicine involves running expensive tests called genomic sequencing, which scan the DNA of tumors to find mutations that might be susceptible to available drugs. Although the field is relatively new, hundreds of thousands of cancer patients have had their tumors sequenced to identify cancer-related mutations, according to testing companies.
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