Lecture 8: Cell Cycle

BIOL 30
Section 23.3: What is the difference between stem cells and cancer cells?

Biology Learning Objectives

• Explain the similarities and differences of cancer cells and stem cells.
• Describe how self-renewal and the cell cycle are regulated in stem cells.
**Cell Cycle Stages**

**Table 3.5** Steps in typical eukaryotic cell cycle.

<table>
<thead>
<tr>
<th>name</th>
<th>description</th>
<th>duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_1$</td>
<td>growth and normal cellular functions</td>
<td>10</td>
</tr>
<tr>
<td>$S$</td>
<td>synthesis of DNA</td>
<td>8</td>
</tr>
<tr>
<td>$G_2$</td>
<td>growth and normal cellular functions</td>
<td>4</td>
</tr>
<tr>
<td>mitosis</td>
<td>separation of chromosomes</td>
<td>2</td>
</tr>
</tbody>
</table>

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Cell Cycle

- **G₂**: The cell “double checks” the duplicated chromosomes for error, making any needed repairs.
- **S**: Each of the 46 chromosomes is duplicated by the cell.
- **G₁**: Cellular contents, excluding the chromosomes, are duplicated.
- **G₀**: Cell cycle arrest.

http://www2.le.ac.uk/departments/genetics/vgec/diagrams/22-Cell-cycle.gif
What types of cells would you expect to remain in $G_0$?

A. Blood cells
B. Heart muscle cells
C. Epithelial cells
D. Both A and C
E. None of the above
What types of cells would you expect to remain in $G_0$?

A. Blood cells
B. Heart muscle cells
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E. None of the above

Cells that don’t divide often
- Neurons
- Cardiac muscle cells
What type of cells do you expect to divide often?

A. Skin cells
B. Gut epithelial cells
C. Kidney cells
D. Both A and B
E. None of the above
What type of cells do you expect to divide often?

A. Skin cells
B. Gut epithelial cells
C. Kidney cells
D. Both A and B
E. None of the above
What type of cells do you expect to divide often?

- Cells with rapid turn-over
  - Gut epithelial cells
  - Blood cells
  - Skin cells

- Embryonic stem cells
  - During development

- Cancer cells
  - Don’t stop at normal cell cycle checkpoints
Development of stem cells

Stem cells are involved in embryonic and adult cell growth and differentiation

Figure 23.12

Figure 1a and b from Taipale & Beachy, 2001, Reprinted by permission from Macmillan Publishers Ltd.
Development of stem cells

Stem cells give rise to tissue-specific stem cells

These give rise to progenitor cells, which mature into differentiated cells.

Figure 23.12

Figure 1a and b from Taipale & Beachy, 2001, Reprinted by permission from Macmillan Publishers Ltd.
What type of cells can neural stem cells become?

A. Neurons
B. Bone cells
C. Embryonic Stem Cells
D. Only Neurons and Neural Stem Cells
E. All of the above
What type of cells can neural stem cells become?

A. Neurons
B. Bone cells
C. Embryonic Stem Cells
D. Only Neurons and Neural Stem Cells
E. All of the above
Partial schematic cartoon of cell cycle regulation in adult stem cells

Figure 23.13

He et al. 2009 Figure 2c, modified with permission from the Annual Review of Cell and Developmental Biology.
Cell cycle regulation in adult stem cells

Mitogen activates cell cycle

Figure 23.14

He et al. 2009 Figure 2c, modified with permission from the Annual Review of Cell and Developmental Biology.
Cell cycle regulation in adult stem cells

Pink = proto-oncogene (codes for proteins that regulate growth and differentiation; cause cancer when mutated or expression increases) proteins

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Cell cycle regulation in adult stem cells

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Purple = tumor suppressors (genes or proteins that protect cells from cancer, and when mutated can cause cells to progress to cancer)

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Cell cycle regulation in adult stem cells

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Cell cycle regulation in adult stem cells

“P” denotes phosphorylation

Phases of the cell cycle

Figure 23.14

He et al. 2009 Figure 2c, modified with permission from the Annual Review of Cell and Developmental Biology.
Cell cycle regulation in adult stem cells

What do you predict will happen to cell cycle if you eliminate Bmi-1?

A. The cell will be more likely to pass the restriction point

B. The cell will be less likely to pass the restriction point

C. No change in likelihood of passing the restriction point

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He et al. 2009 Figure 2c, modified with permission from the Annual Review of Cell and Developmental Biology.
Cell cycle regulation in adult stem cells

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Figure 23.14

He et al. 2009 Figure 2c, modified with permission from the Annual Review of Cell and Developmental Biology.
Effects of loss of \textit{Bmi-1} on stem cell colony proliferation, cell death and BrdU incorporation

CNS stem cells from newborn mice dissociated and plated in cultures, and the number of cells per colony was counted after 4, 7 and 14 d.

From Molofsky et al., 2003, Figure 2, reprinted by permission from Macmillan Publishers Ltd.
Elimination of which protein is most likely to lead to increased progression through the cell cycle (and potentially cancer)?

A. Cyclin D

B. p53

C. Hmga2

D. p53 and Hmga2

Figure 23.14

He et al. 2009 Figure 2c, modified with permission from the Annual Review of Cell and Developmental Biology.
Elimination of which protein is most likely to lead to increased progression through the cell cycle (and potentially cancer)?

A. Cyclin D
B. p53
C. Hmga2
D. p53 and Hmga2

He et al. 2009 Figure 2c, modified with permission from the Annual Review of Cell and Developmental Biology.
What is the connection between stem and cancer cells?

• Each cell type exists as a population
• Populations of cells in animals have evolved complex mechanisms of regulation, which can become dysfunctional

• Cancer cells have properties similar to stem cells
• Self-renewal and cell cycle in stem cells is regulated
• In cancer, cell cycle is unregulated or dysfunctional
• Cancer caused by many factors; tumors may originate from transformation of signaling pathways in stem cells
Hallmarks of Cancer

Malignant versus Benign Tumors

Benign (not cancer) tumor cells grow only locally and cannot spread by invasion or metastasis.

Malignant (cancer) cells invade neighboring tissues, enter blood vessels, and metastasize to different sites.

Time

Cancer Case Study

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What is one hypothesis you can make based on this data?
Observation: Intracellular pH is Higher in Cancer Cells

Normal epithelium

Transformation/Dysplasia

Metastasis

What is one hypothesis you can make based on this data?

- Increasing intracellular pH can cause cancer
- Decreasing intracellular pH in cancer cells can be used to treat cancer
Intracellular pH (pH\textsubscript{i}) Regulation

- H+ ions produced by cellular metabolism
- H+ ions transported out of the cell by ion transporters, notably the Na+/H+ Exchanger (NHE)
If you increased the number of NHE transporters, what effect on pH\textsubscript{i} do you expect?

A. Increased pH\textsubscript{i}
B. Decreased pH\textsubscript{i}
C. More basic pH\textsubscript{i}
D. Both A and C
E. No change in pH\textsubscript{i}
If you increased the number of NHE transporters, what effect on pH\textsubscript{i} do you expect?

A. Increased pH\textsubscript{i}
B. Decreased pH\textsubscript{i}
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Hypothesis: Overexpression of NHE will lead to cancer

• Use fly model where genes can be easily inserted, over or under expressed

• Measure abnormal cell proliferation (number) as output for ‘cancer’

• Also test whether oncogene expression can enhance the effect of NHE overexpression
  – Oncogenes (like Ras) cause cancer when mutated or overexpressed
Which treatments increase cell proliferation (proliferating cells shown in green)?

Control +NHE +Ras (Oncogene) +NHE & Ras
A. +NHE
B. +Ras
C. +Ras and NHE
D. B & C
E. A, B, & C

Which treatments increase cell proliferation (proliferating cells shown in green)?

Control +NHE +Ras (Oncogene) +NHE & Ras

A. +NHE  
B. +Ras  
C. +Ras and NHE  
D. B & C  
E. A, B, & C

What conclusion can you draw from these data?

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Upregulation of NHE alone doesn’t have an effect, but NHE upregulation can increase the effectiveness of Ras in promoting proliferation.

Can you think of a way to treat cancer based on these findings?
Can you think of a way to treat cancer based on these findings?

Decrease NHE expression to decrease pH,i.
Can inhibiting NHE treat cancer?

<table>
<thead>
<tr>
<th></th>
<th>colon</th>
<th>breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH Control</td>
<td>7.3</td>
<td>7.6</td>
</tr>
<tr>
<td>pH + NHE inhibitor</td>
<td>7.2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

NHE Inhibitors Now in Clinical Trials

Want to learn more?


https://elifesciences.org/content/4/e03270