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.

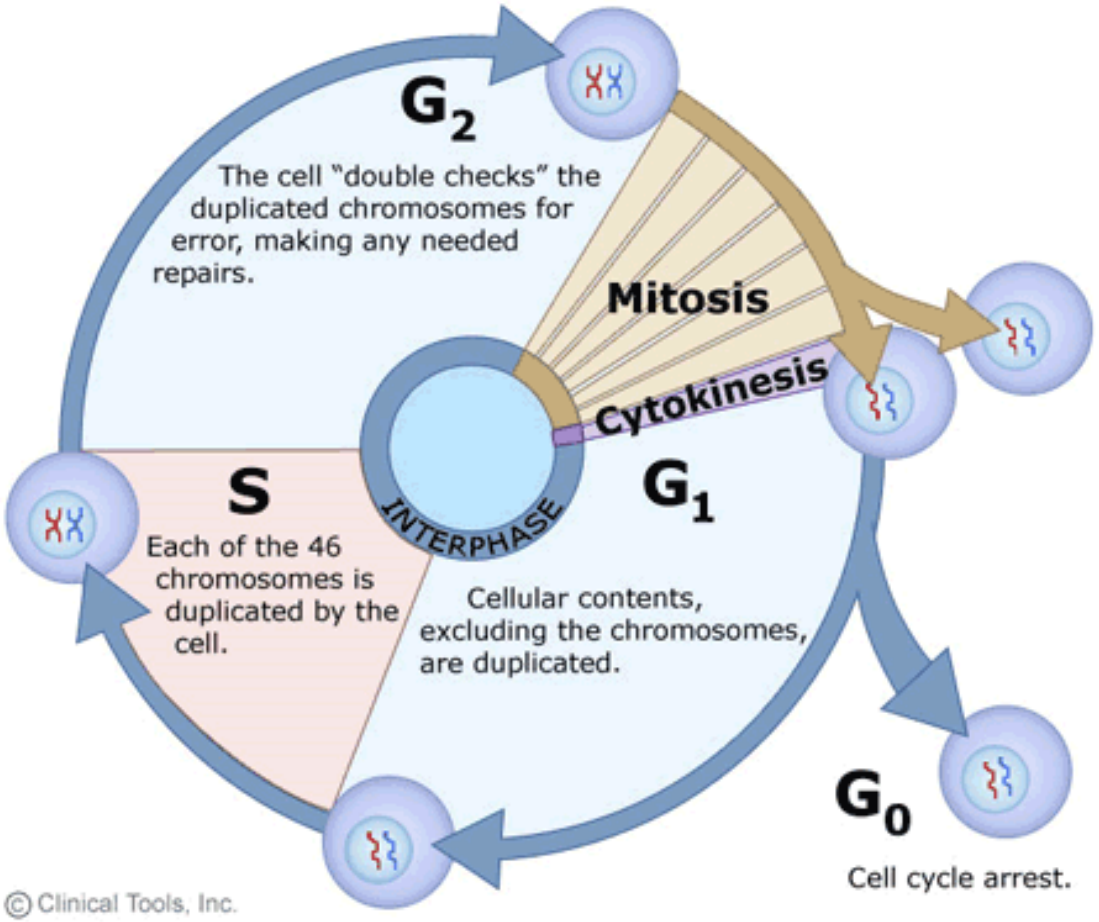
Cell Cycle Stages

Table 3.5 Steps in typical eukaryotic cell cycle.

name	description	duration (hours)
G_1	growth and normal cellular functions	10
S	synthesis of DNA	8
G_2	growth and normal cellular functions	4
mitosis	separation of chromosomes	2

Table 3.5

Cell Cycle



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

C. Epithelial cells

D. Both A and C

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

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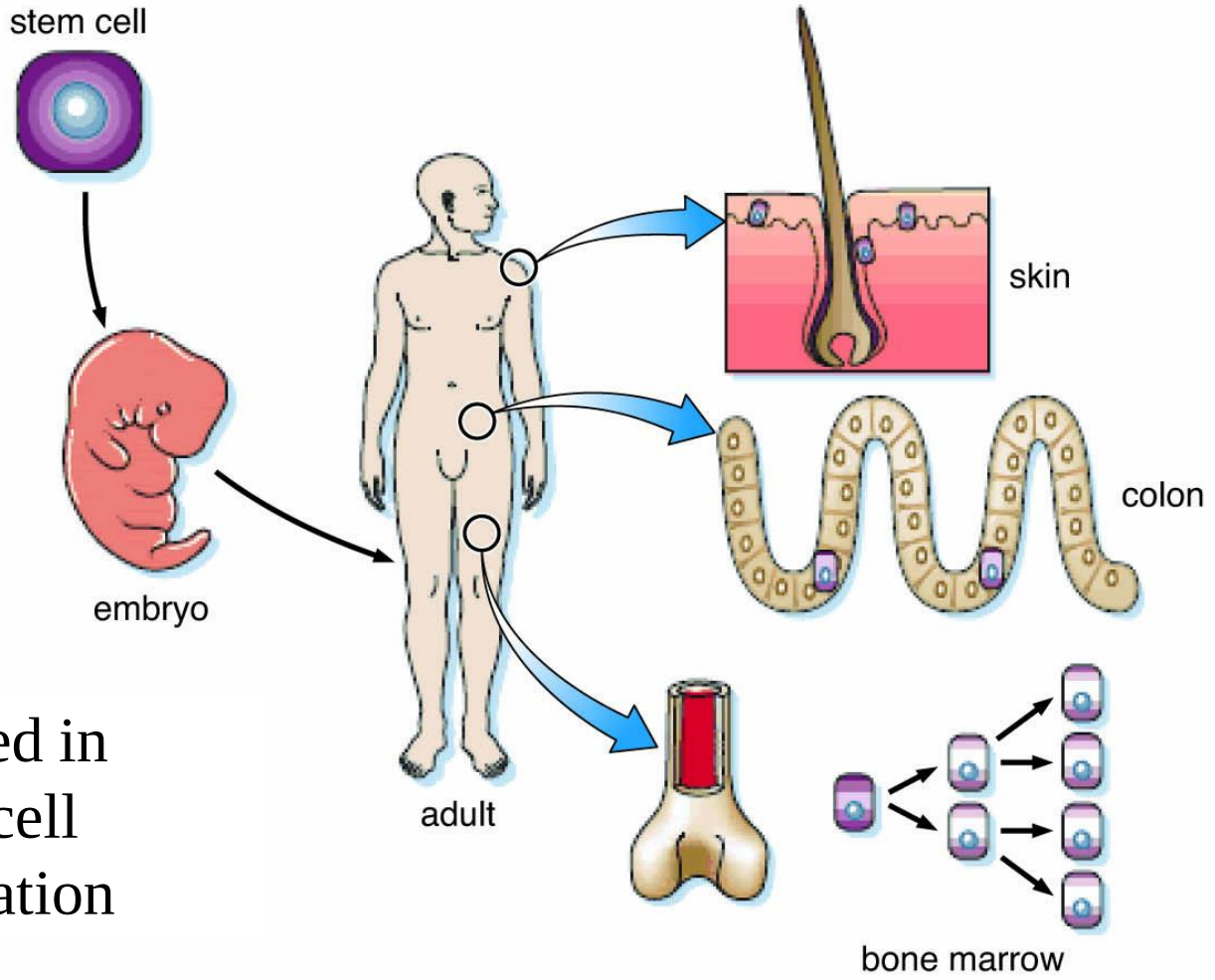
E. None of the above

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

Development of stem cells

Stem cells give rise to tissue-specific stem cells

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

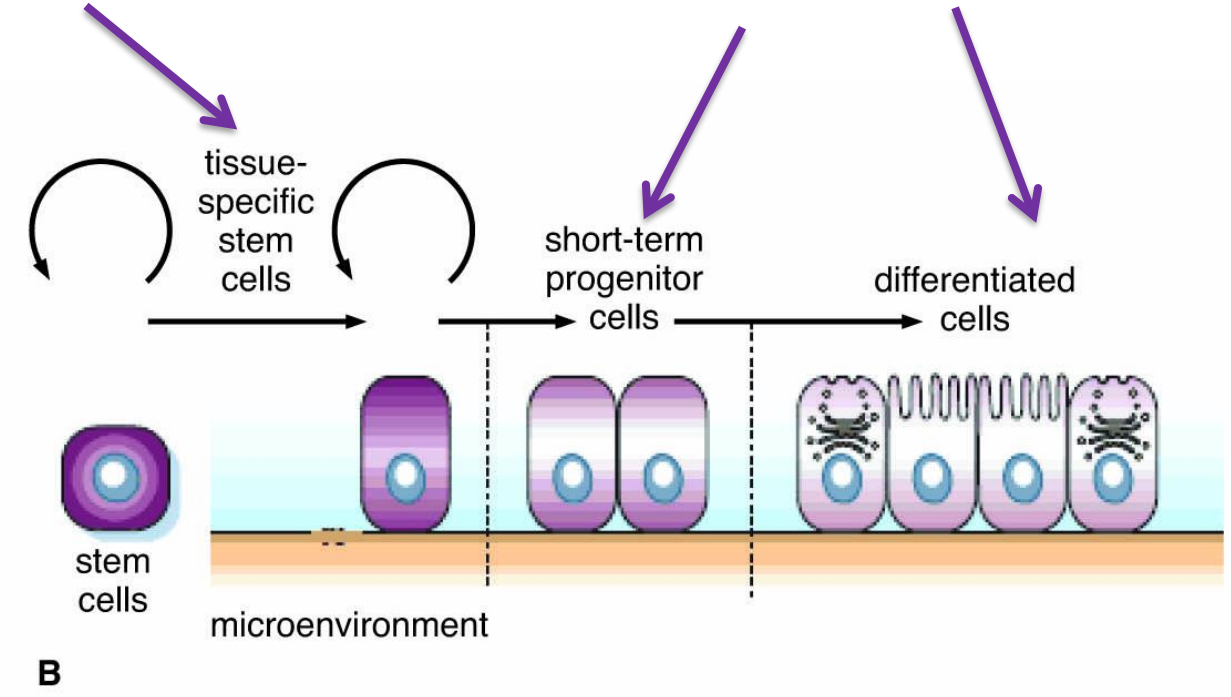


Figure 23.12

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

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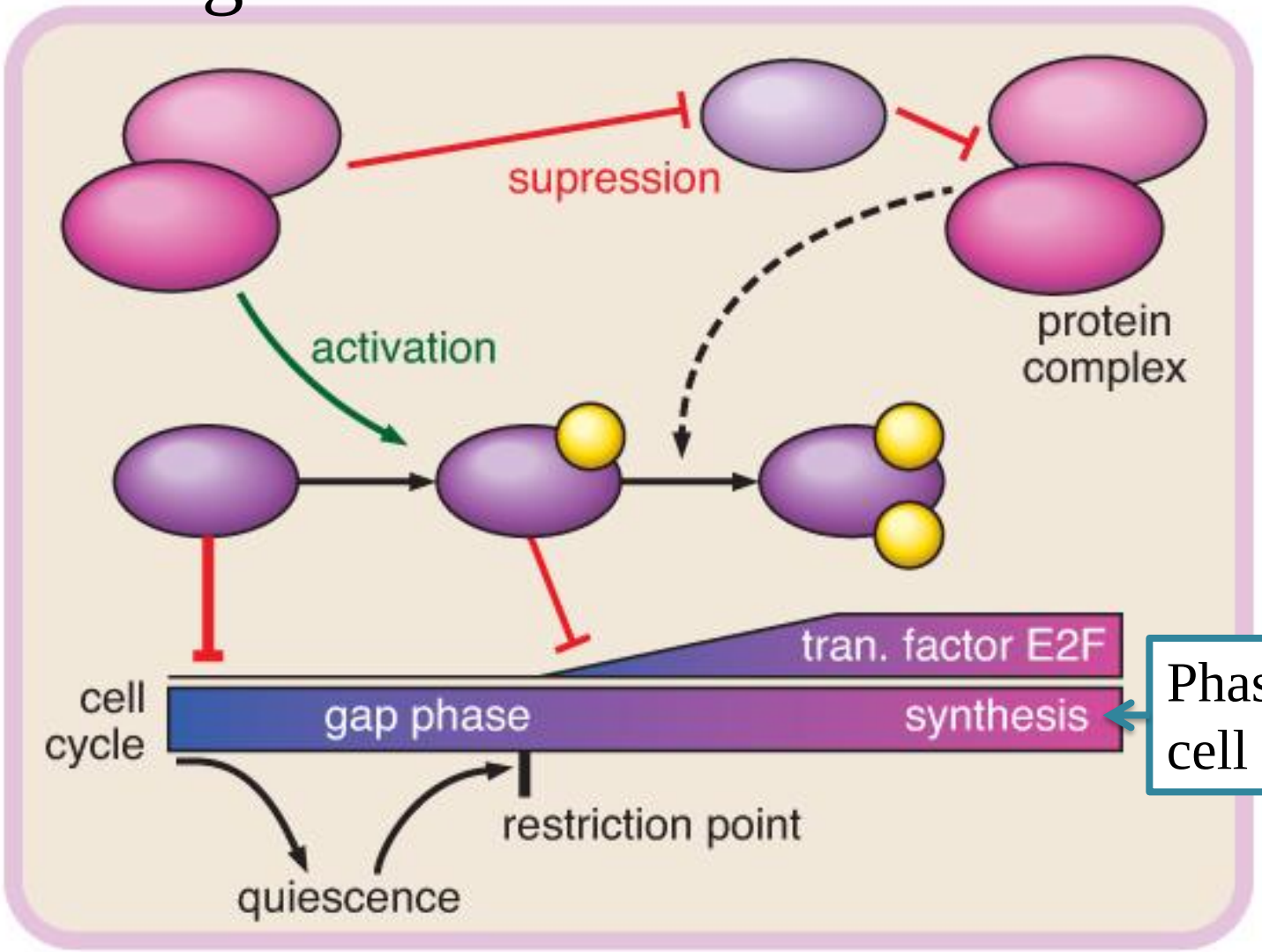
Partial schematic cartoon of cell cycle regulation in adult stem cells

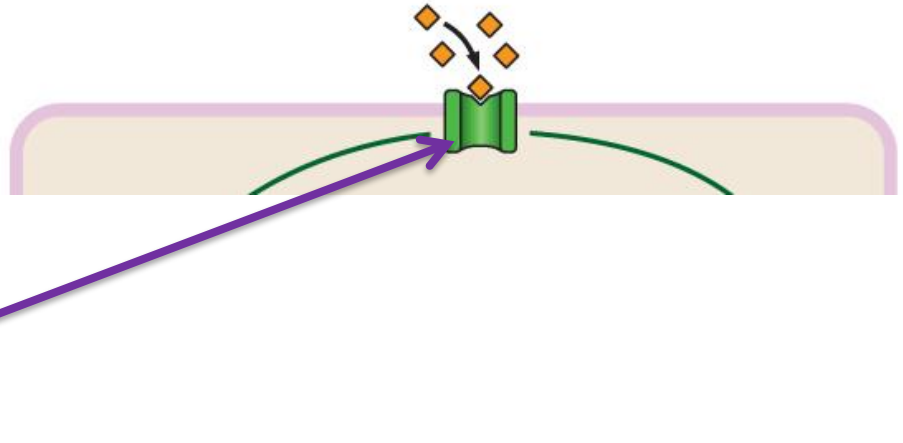


Phases of the cell cycle

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

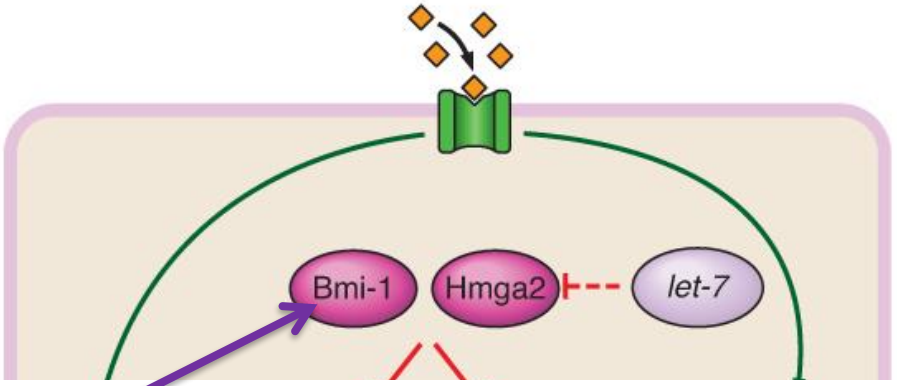


Mitogen activates cell cycle

Figure 23.14

He et al. 2009 Figure 2c, modified with permission from the Annual Review of Cell and Developmental Biology.

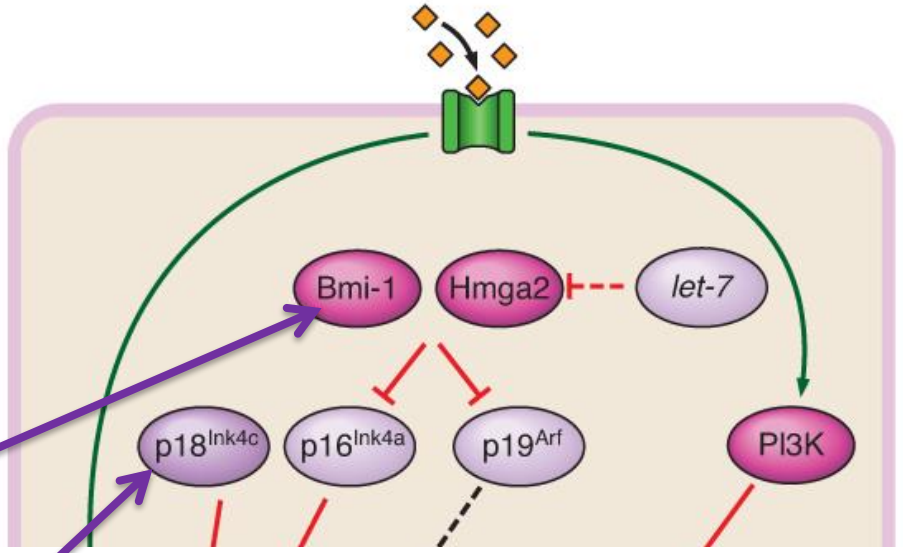
Cell cycle regulation in adult stem cells



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

Figure 23.14

Cell cycle regulation in adult stem cells



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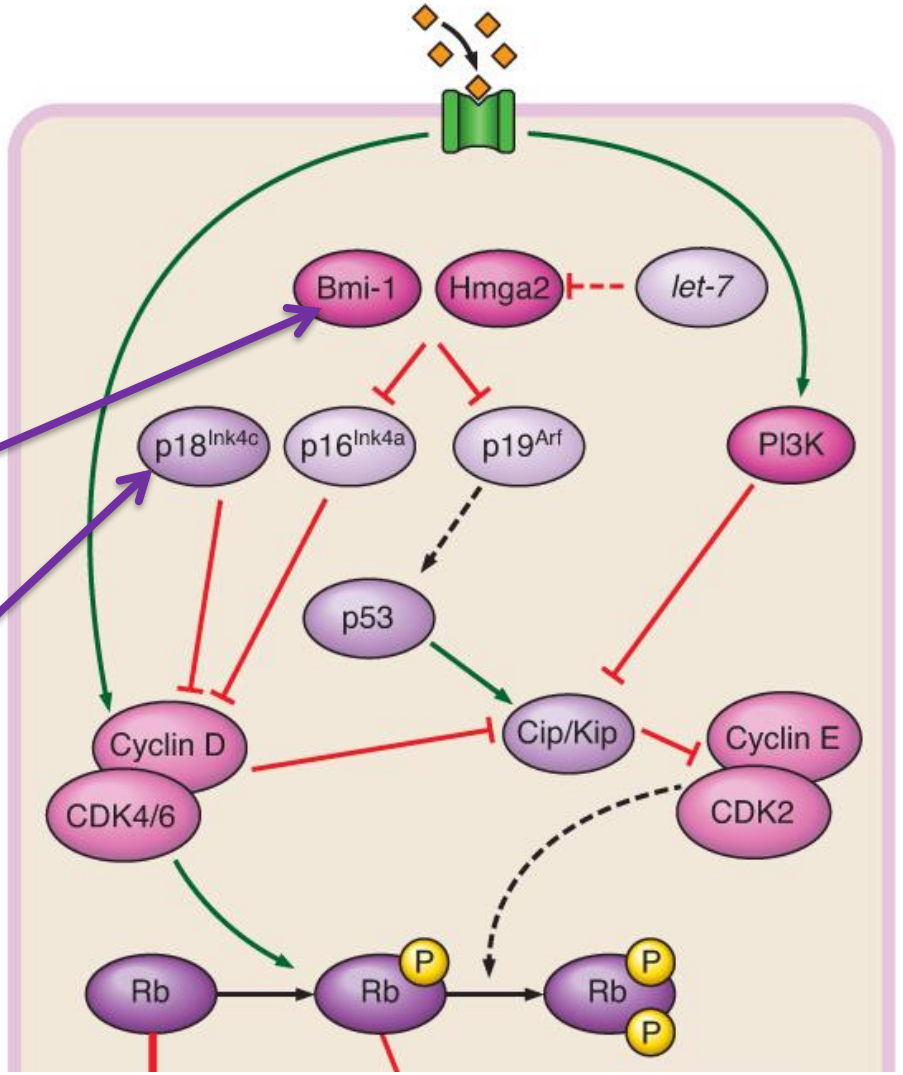
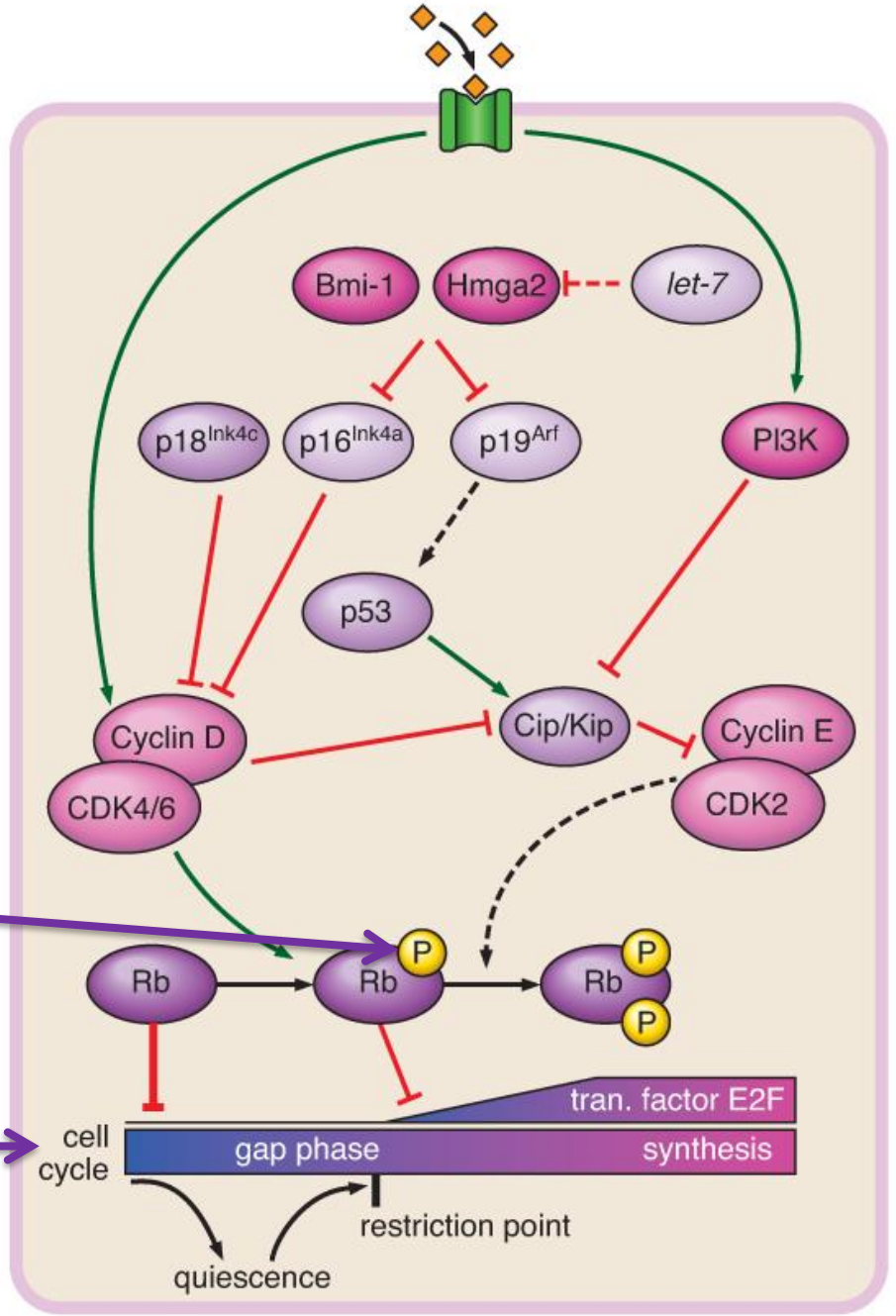


Figure 23.14

Cell cycle regulation in adult stem cells



"P" denotes phosphorylation

Phases of the cell cycle

Figure 23.14

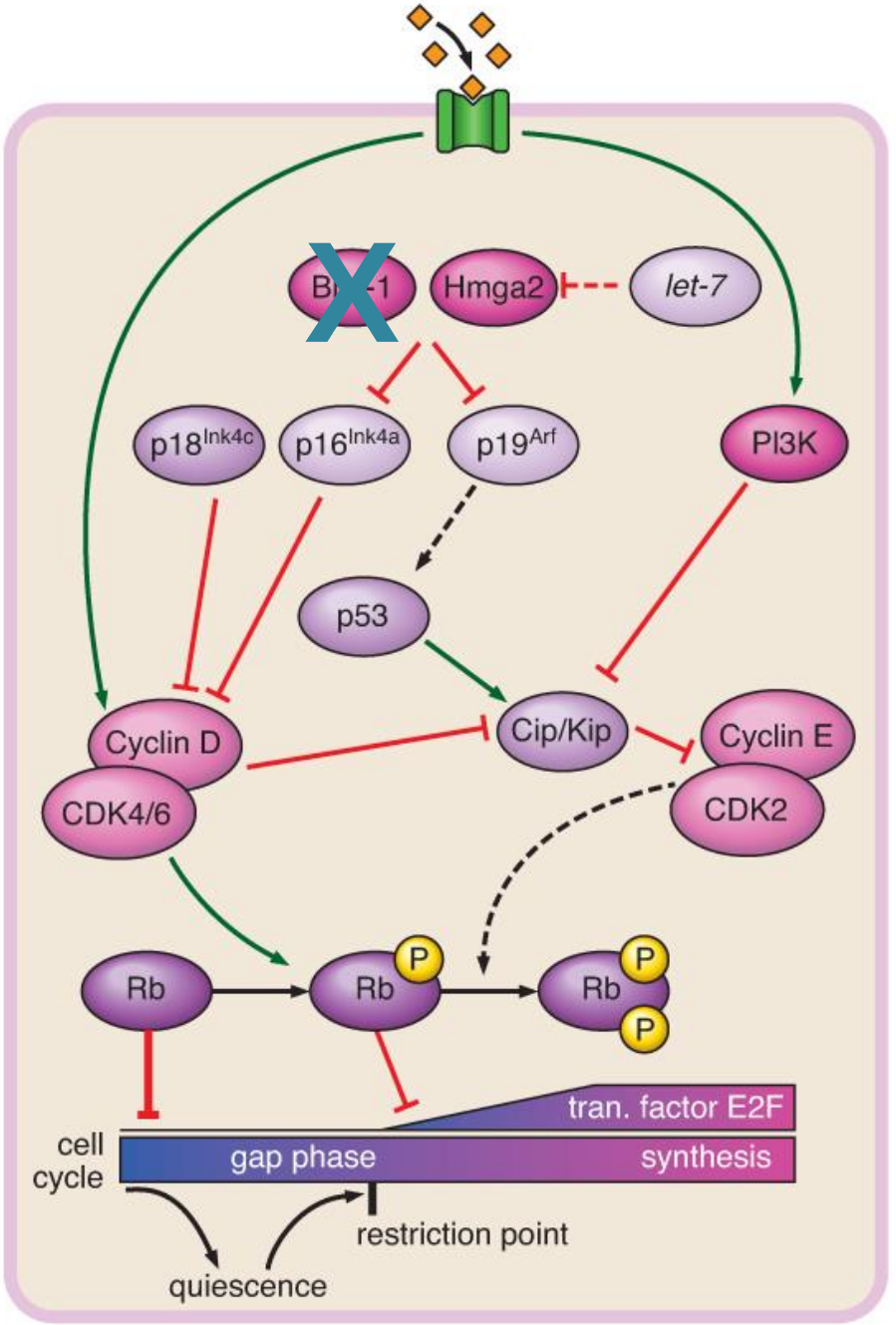
Cell cycle regulation in adult stem cells

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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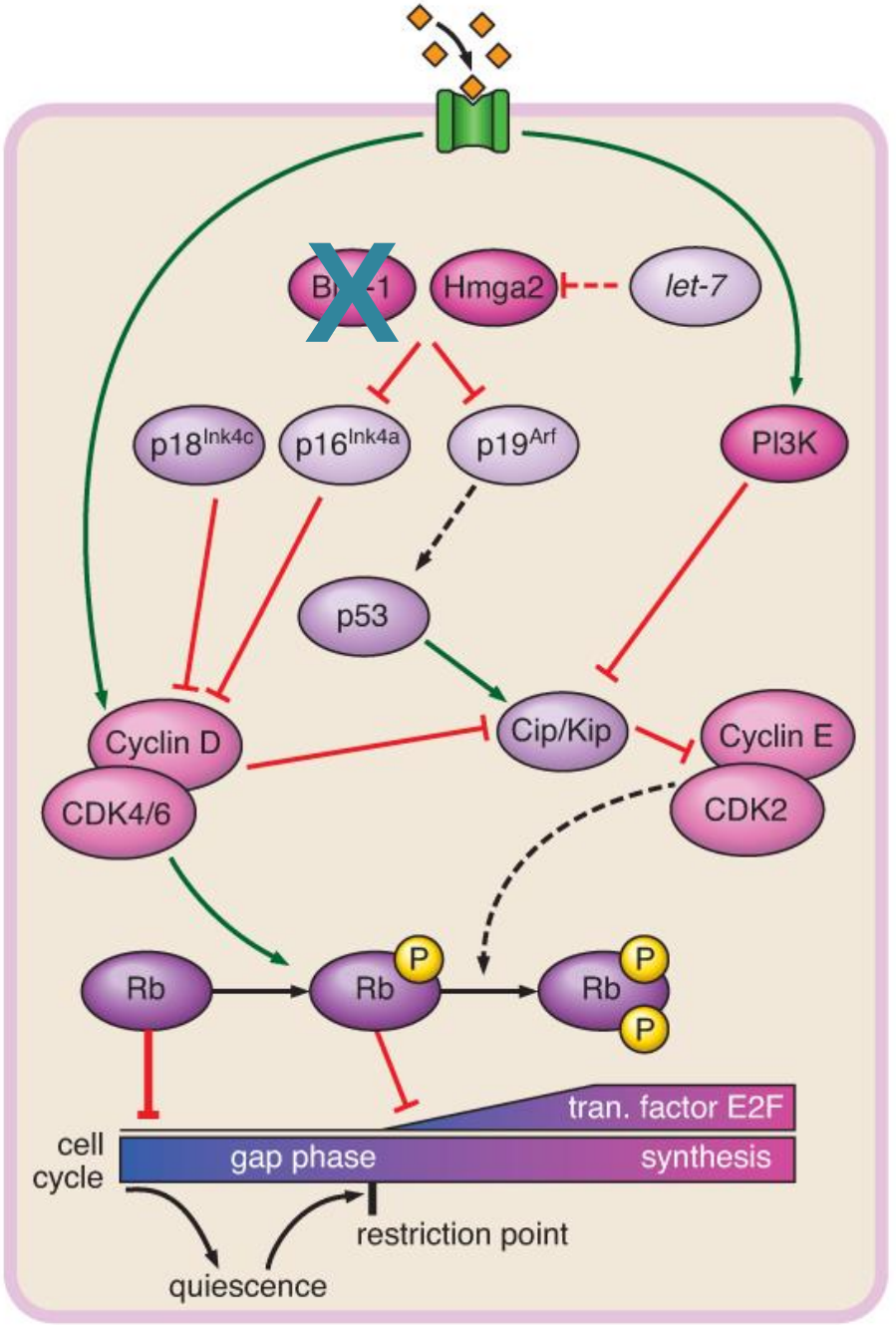
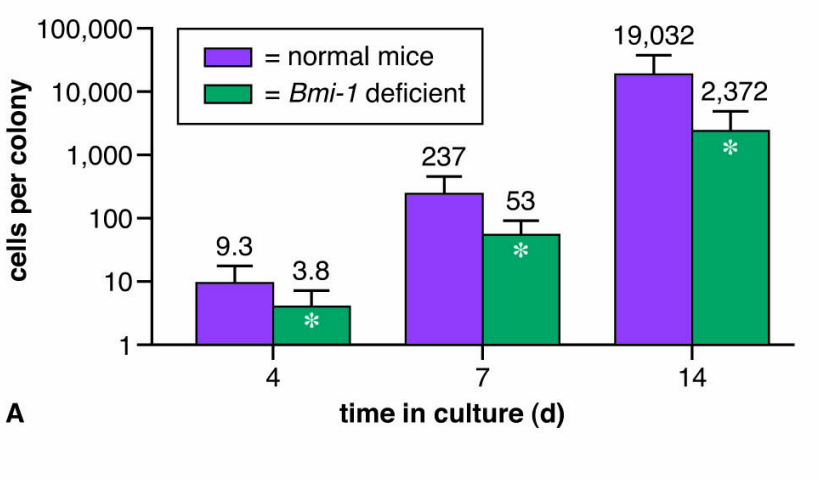


Figure 23.14

Effects of loss of *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.

Figure 23.15

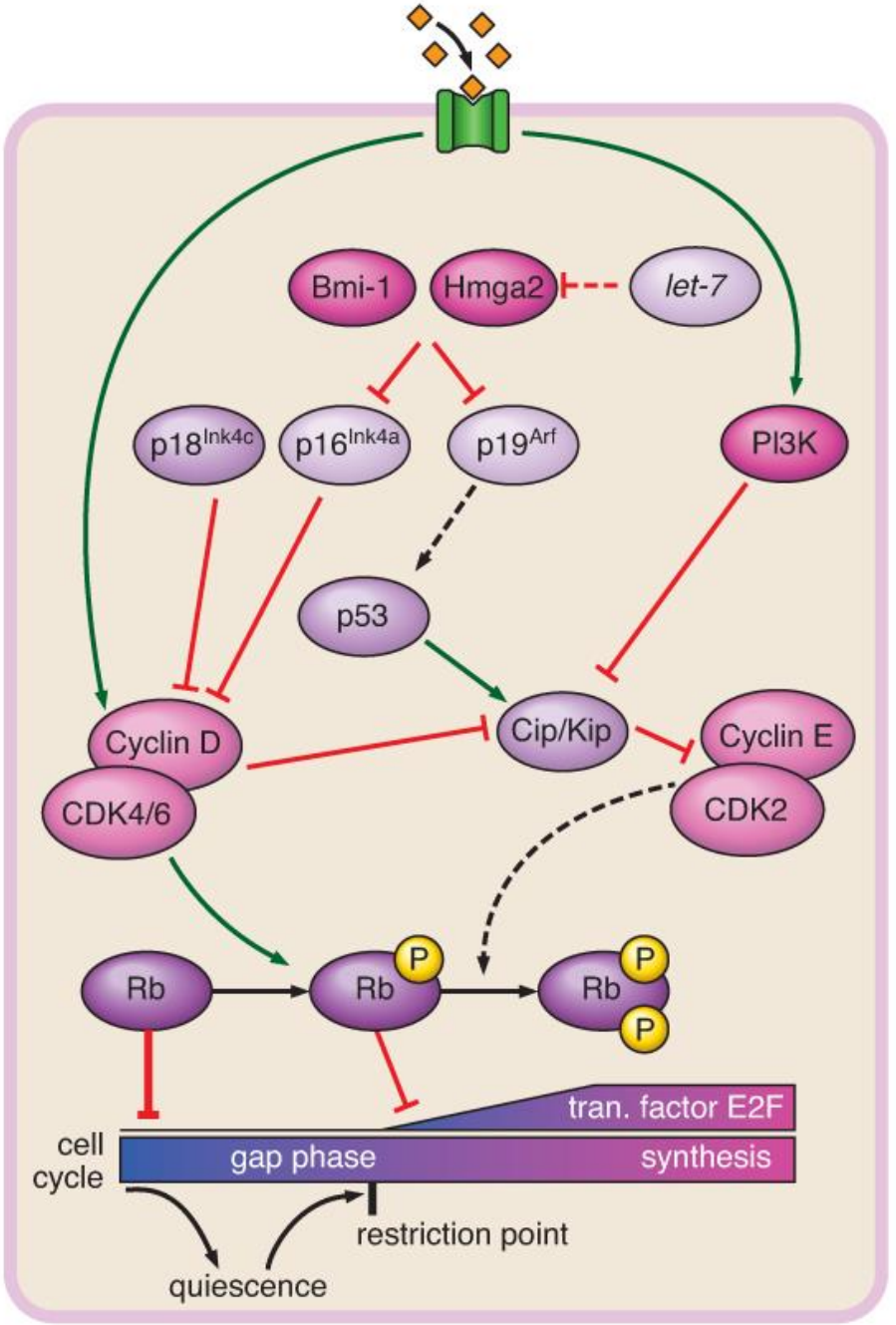
Elimination of which protein is most likely to lead to increased progression through the cell cycle (and potentially cancer)?

A. Cyclin D

B. p53

C. Hmga2

D. p53 and Hmga2



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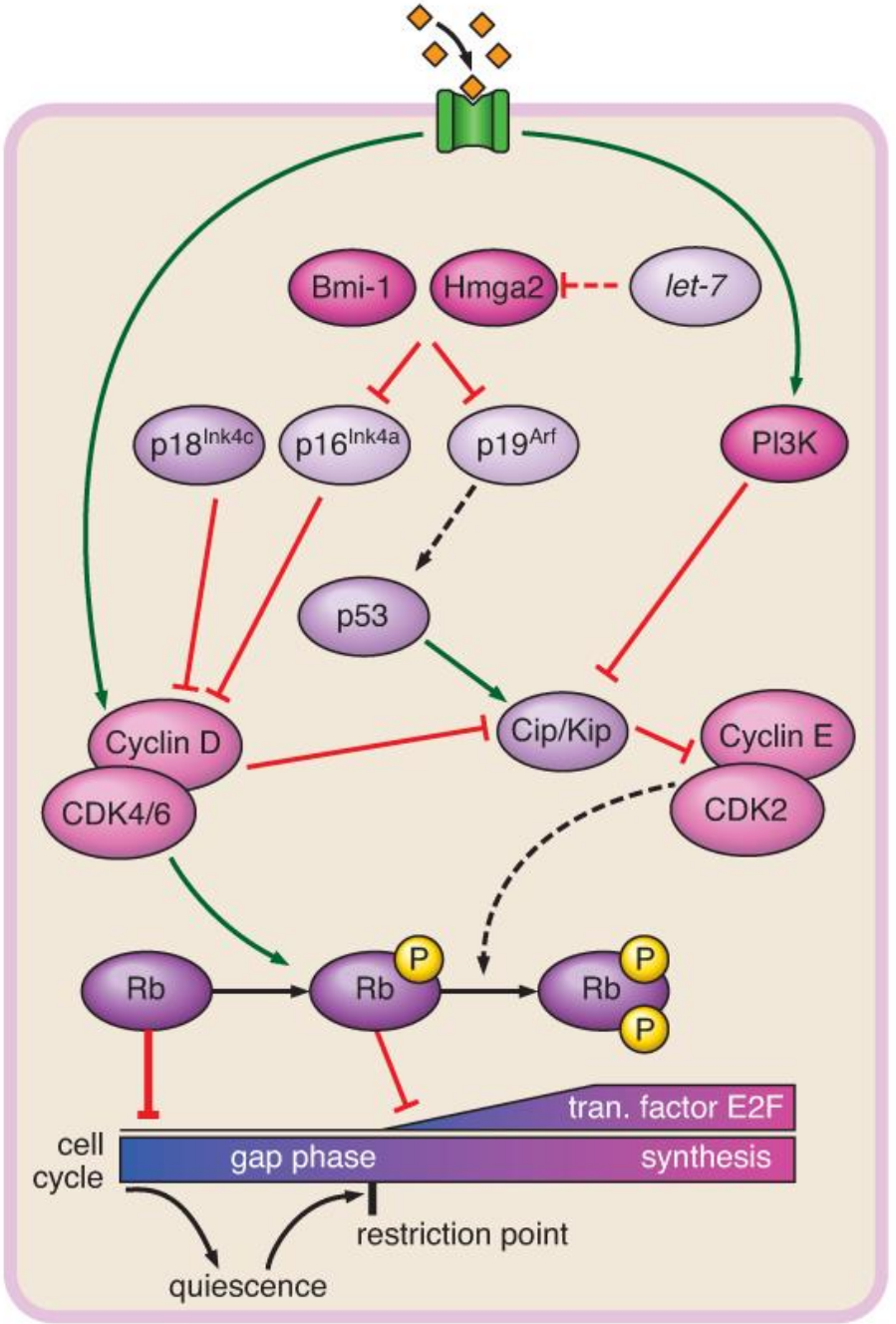


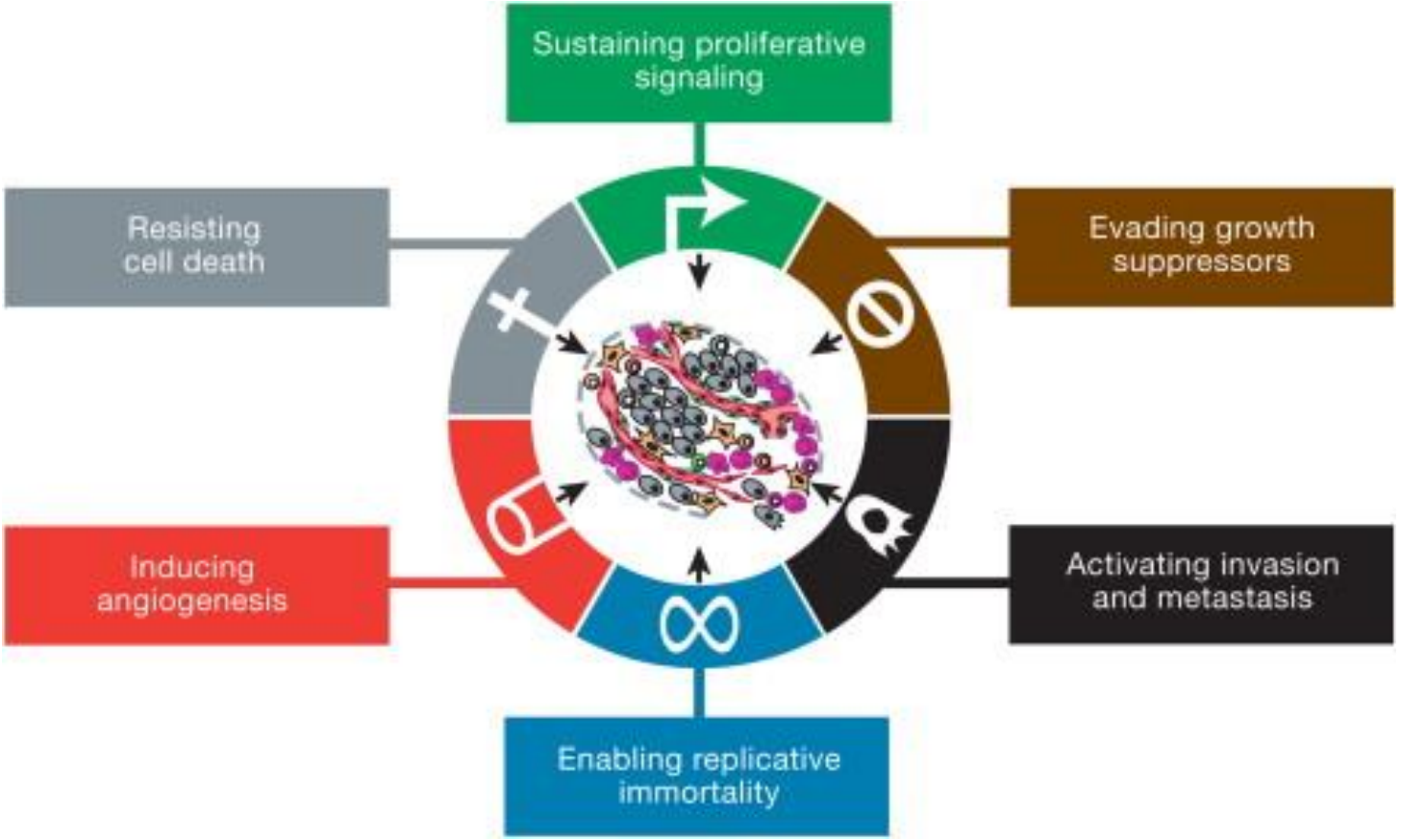
Figure 23.14

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

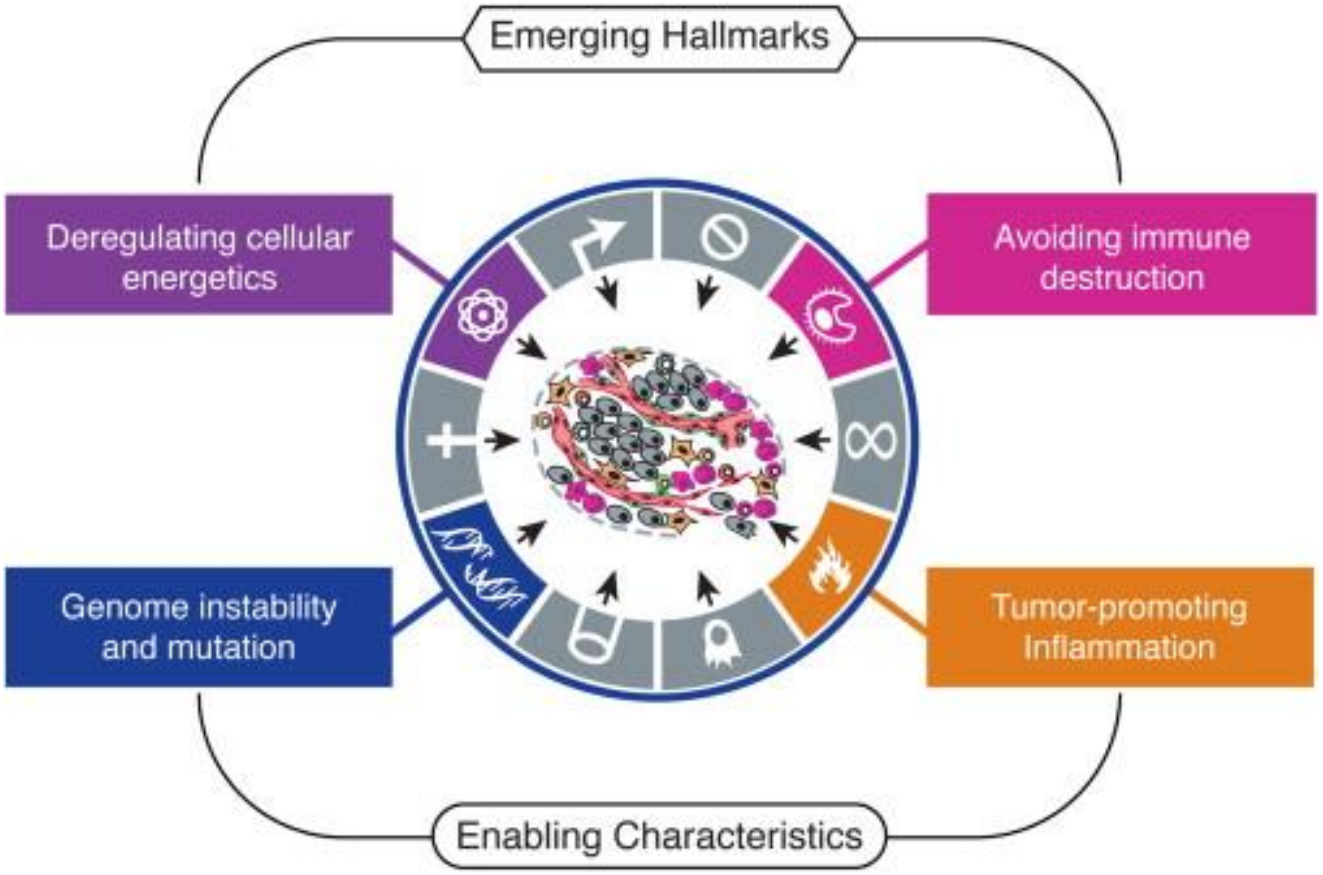
- Cancer cells have properties similar to stem cells
- Self-renewal and cell cycle in stem cells is regulated
- In cancer, cell cycle is unregulated or dysfunctional
- Cancer caused by many factors; tumors may originate from transformation of signaling pathways in stem cells

Hallmarks of Cancer



Hanahan, Douglas, and Robert A. Weinberg. "Hallmarks of cancer: the next generation." cell 144.5 (2011): 646-674.

Hallmarks of Cancer



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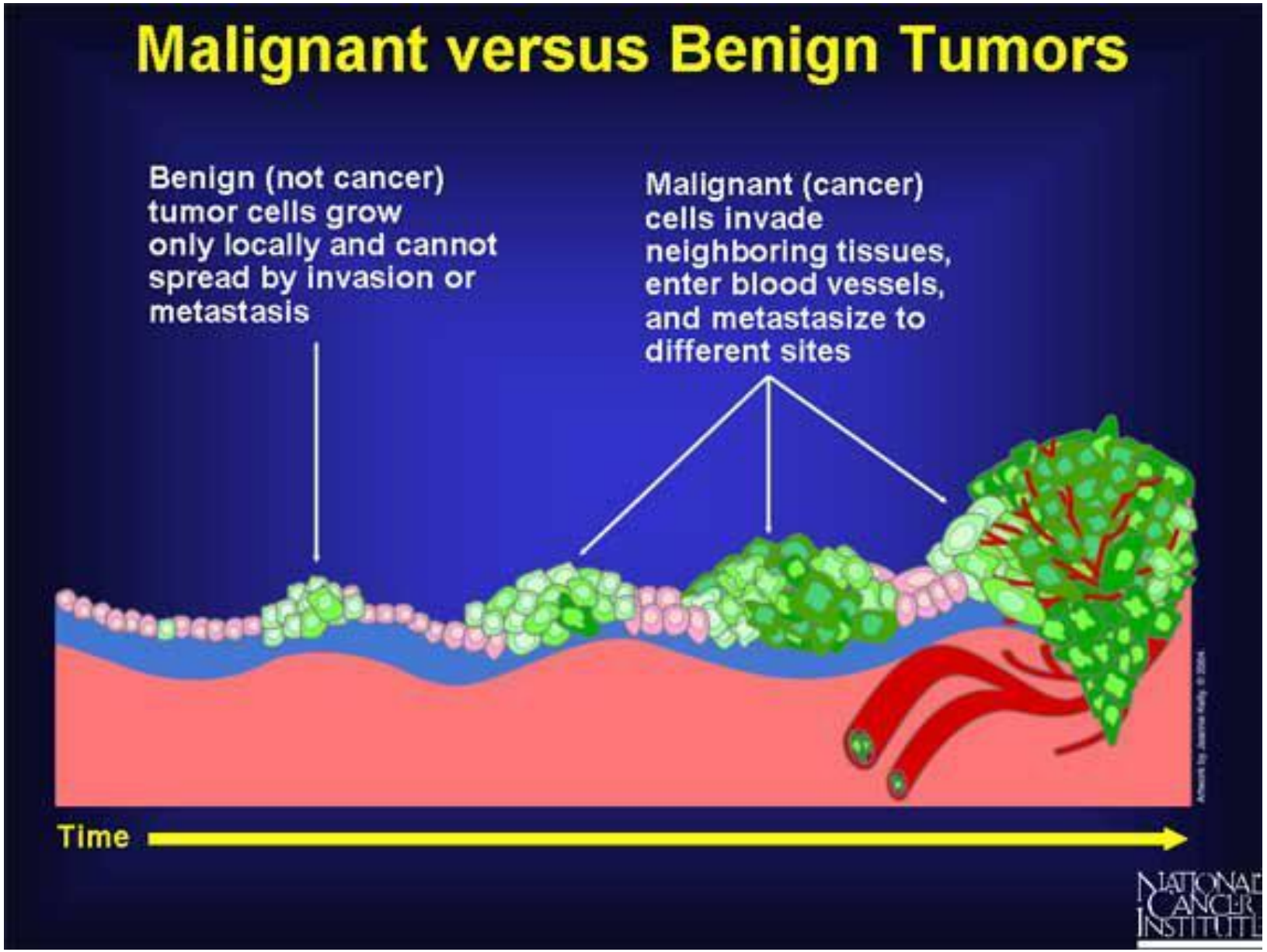

http://www.publichealthunited.org/wp-content/uploads/2013/04/Malignant-v-benign.png

Cancer Case Study

Dr. Bree Grillo-Hill

DH 541

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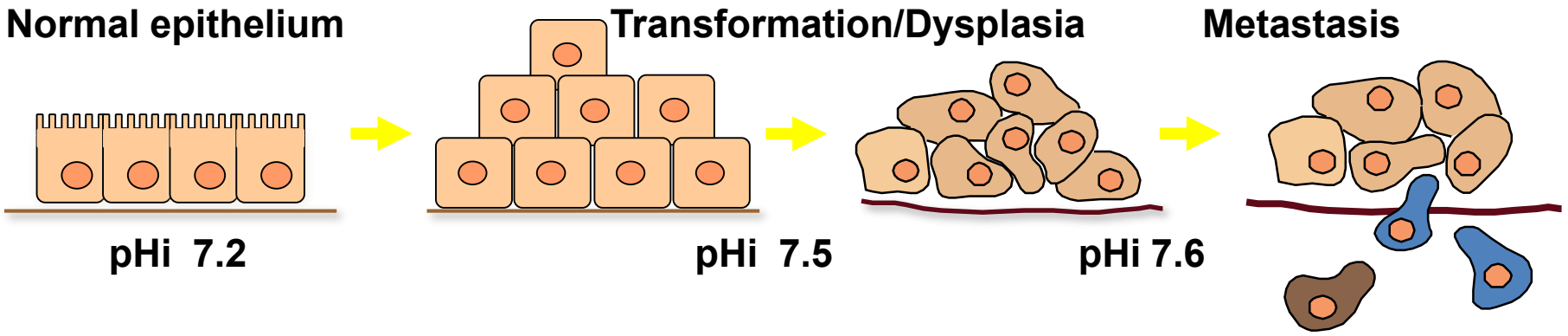
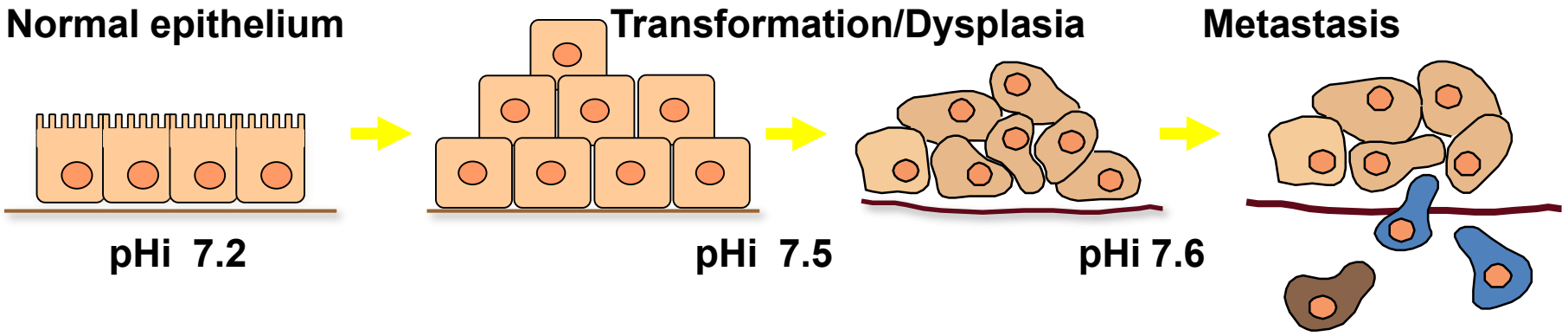
Observation: Intracellular pH is Higher in Cancer Cells



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

Observation: Intracellular pH is Higher in Cancer Cells

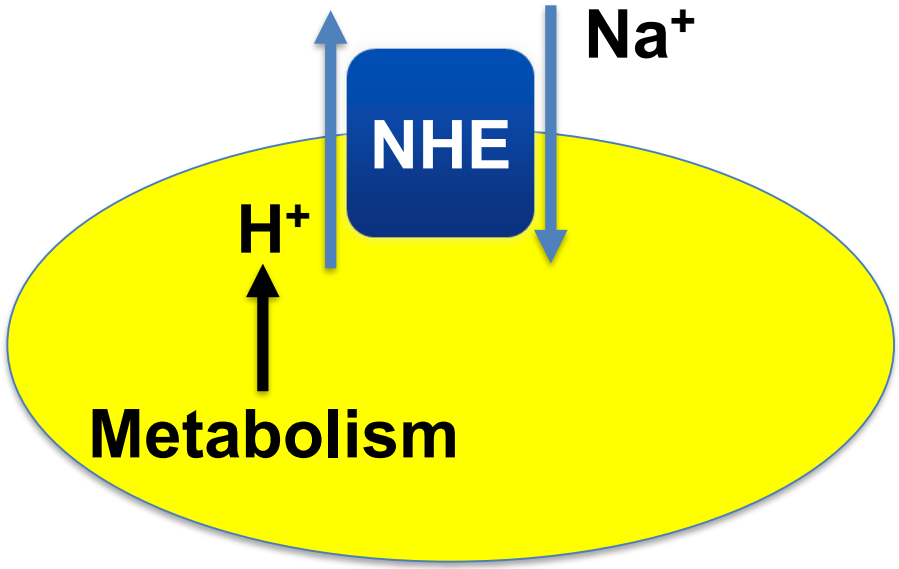


What is one hypothesis you can make based on this data?

- ***Increasing intracellular pH can cause cancer***
- ***Decreasing intracellular pH in cancer cells can be used to treat cancer***

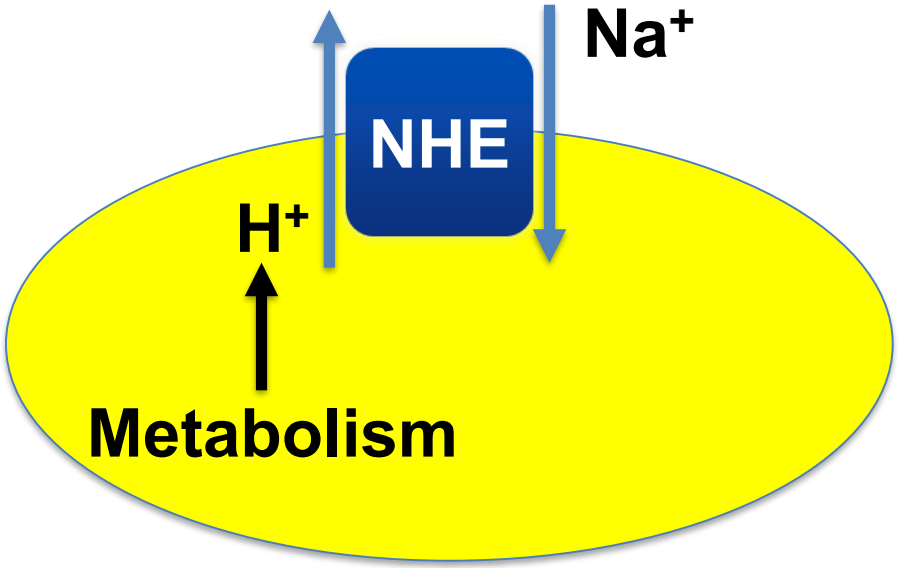
Intracellular pH (pH_i) Regulation

- 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_i do you expect?

A. Increased pH_i
B. Decreased pH_i
C. More basic pH_i
D. Both A and C
E. No change in pH_i



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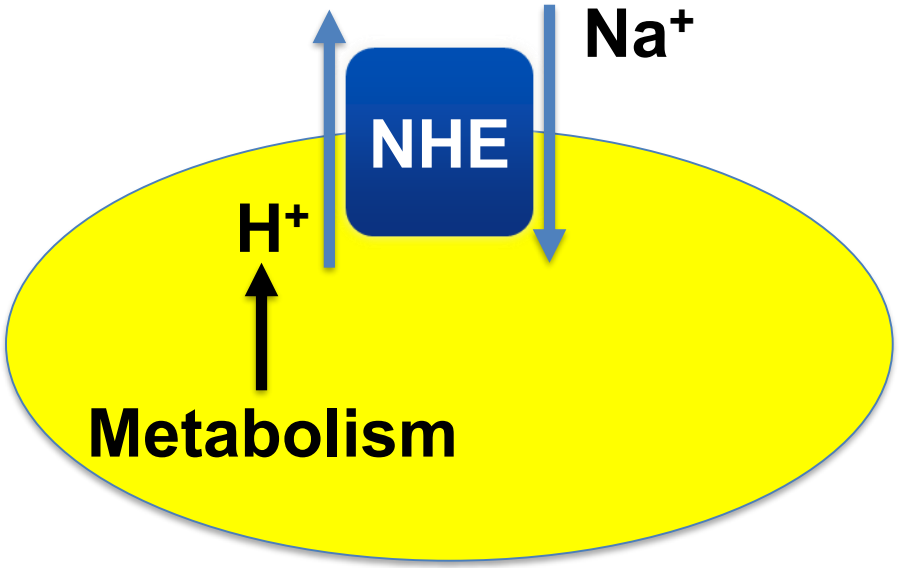


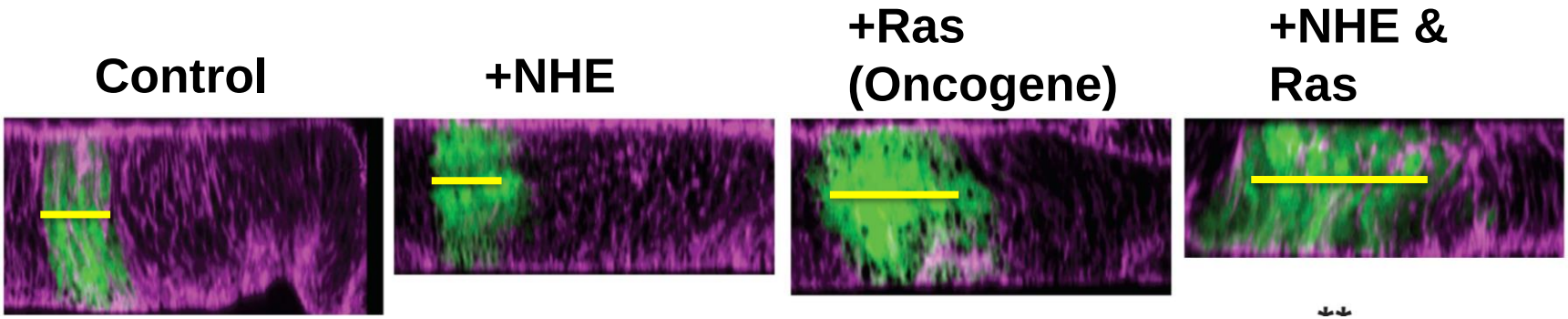
Hypothesis: Overexpression of NHE will lead to cancer

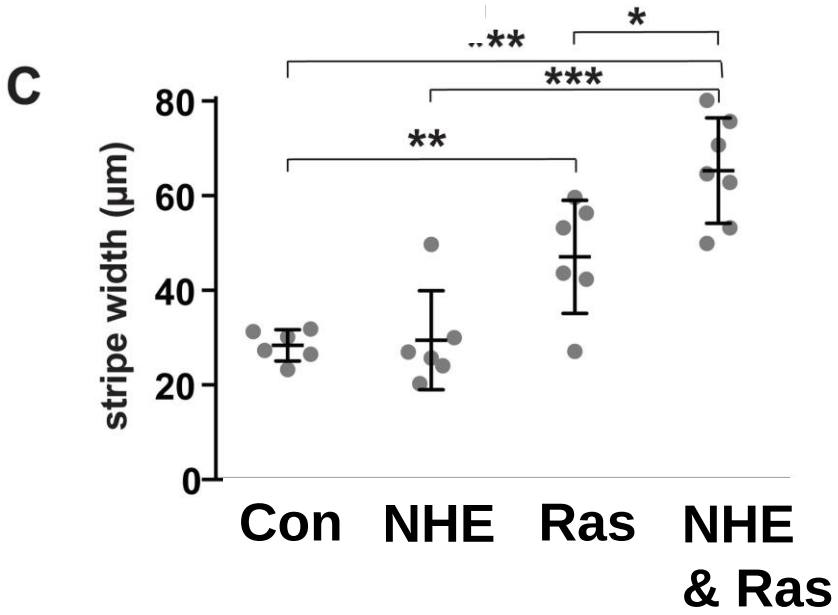
- Use fly model where genes can be easily inserted, over or under expressed

- 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)?





A. +NHE

B. +Ras

C. +Ras and NHE

D. B & C

E. A, B, & C

Grillo-Hill, Bree K., et al. eLife 4 (2015): e03270.

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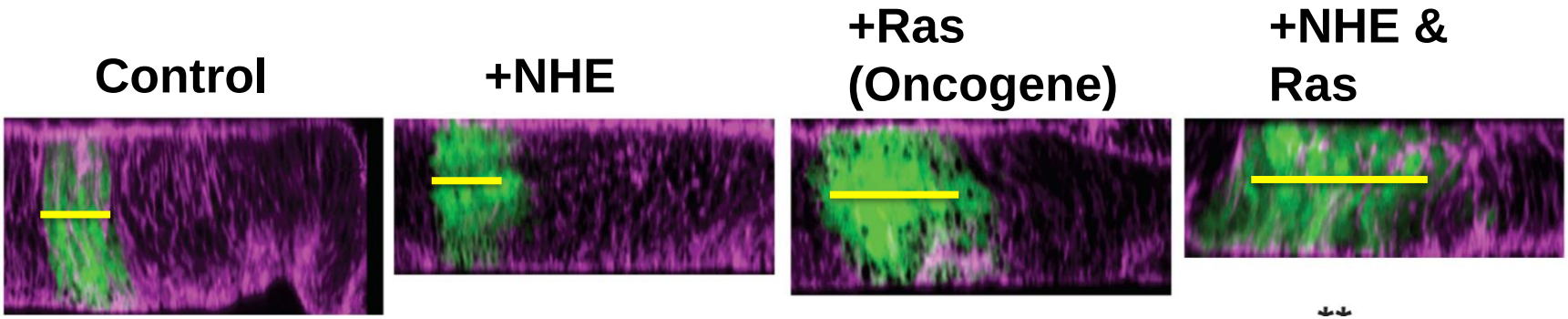

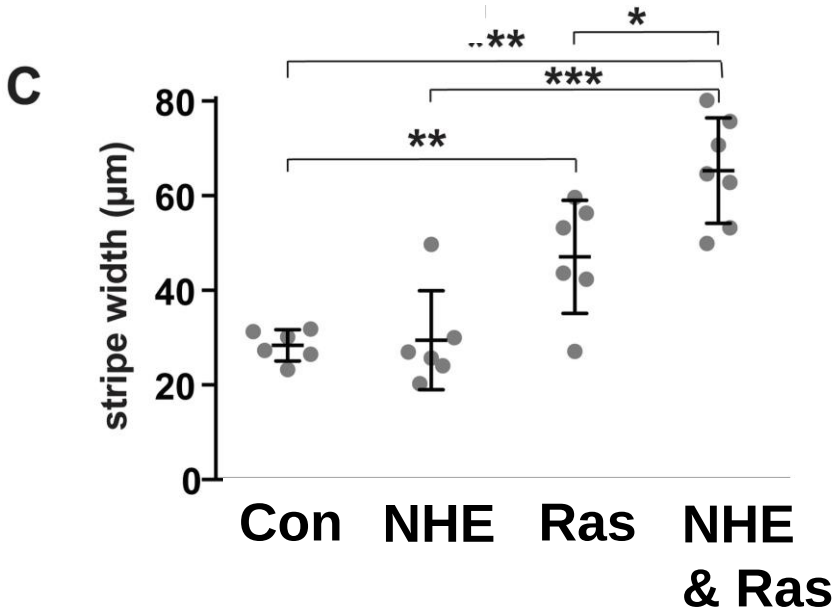

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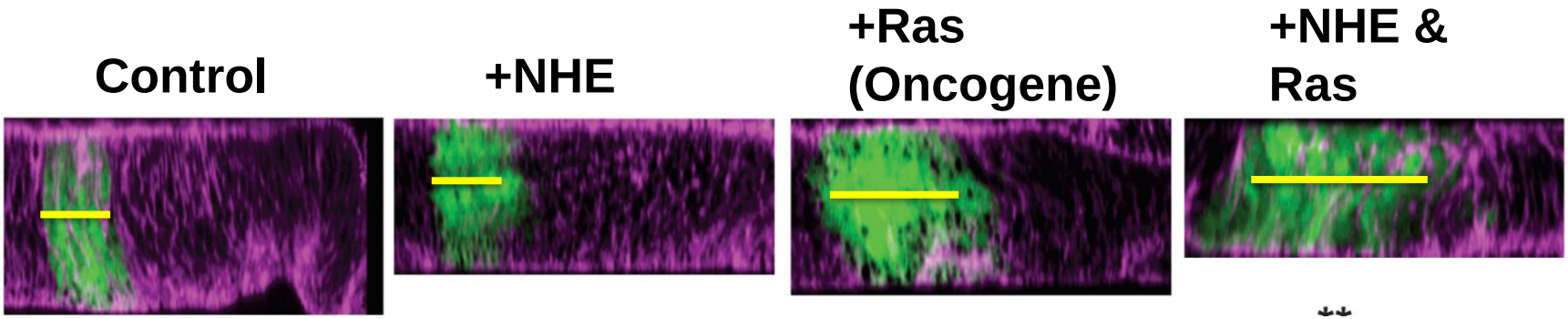
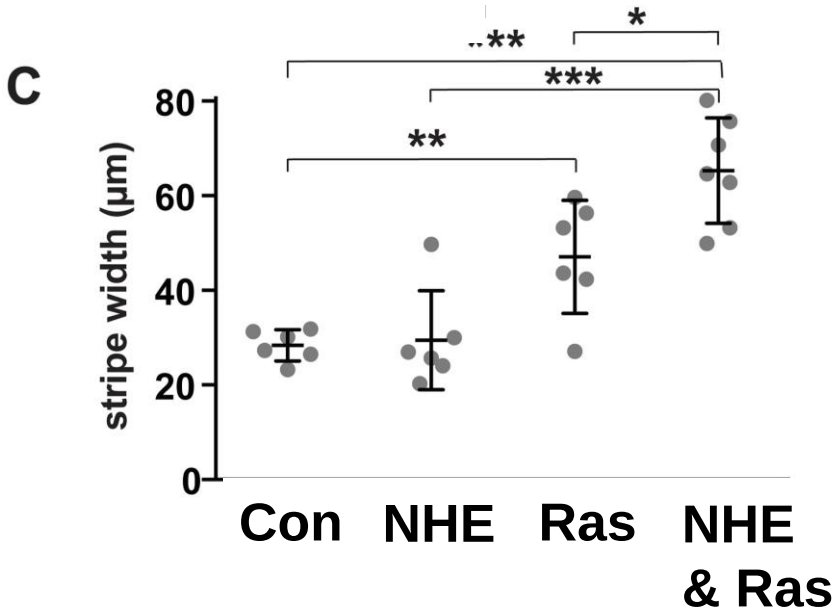
What conclusion can you draw from these data?





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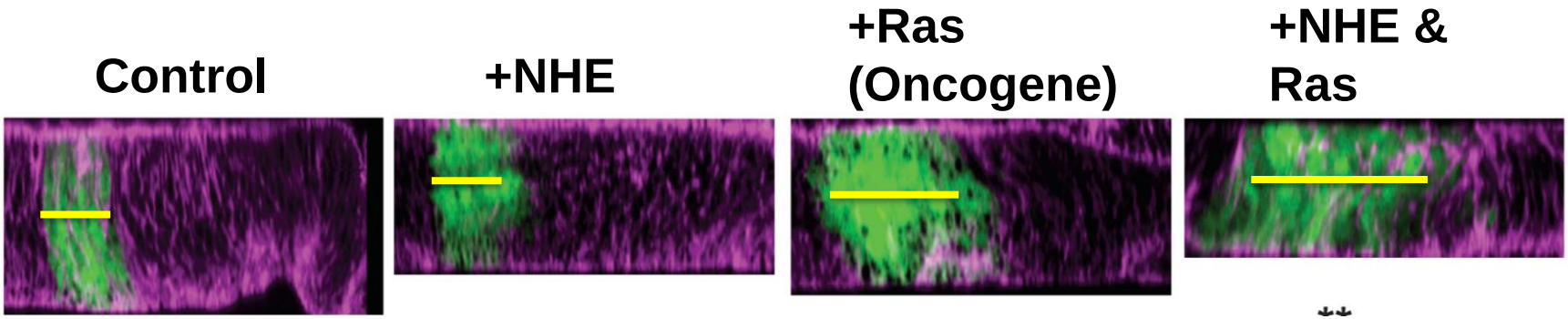

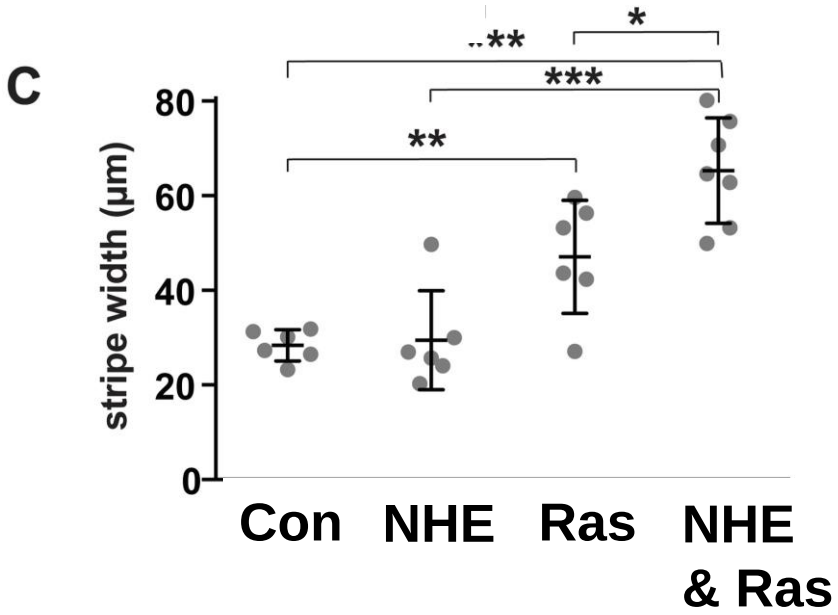

Upregulation of NHE alone doesn't have an effect, but NHE upregulation can increase the effectiveness of Ras in promoting proliferation.

Grillo-Hill, Bree K., et al. eLife 4 (2015): e03270.

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

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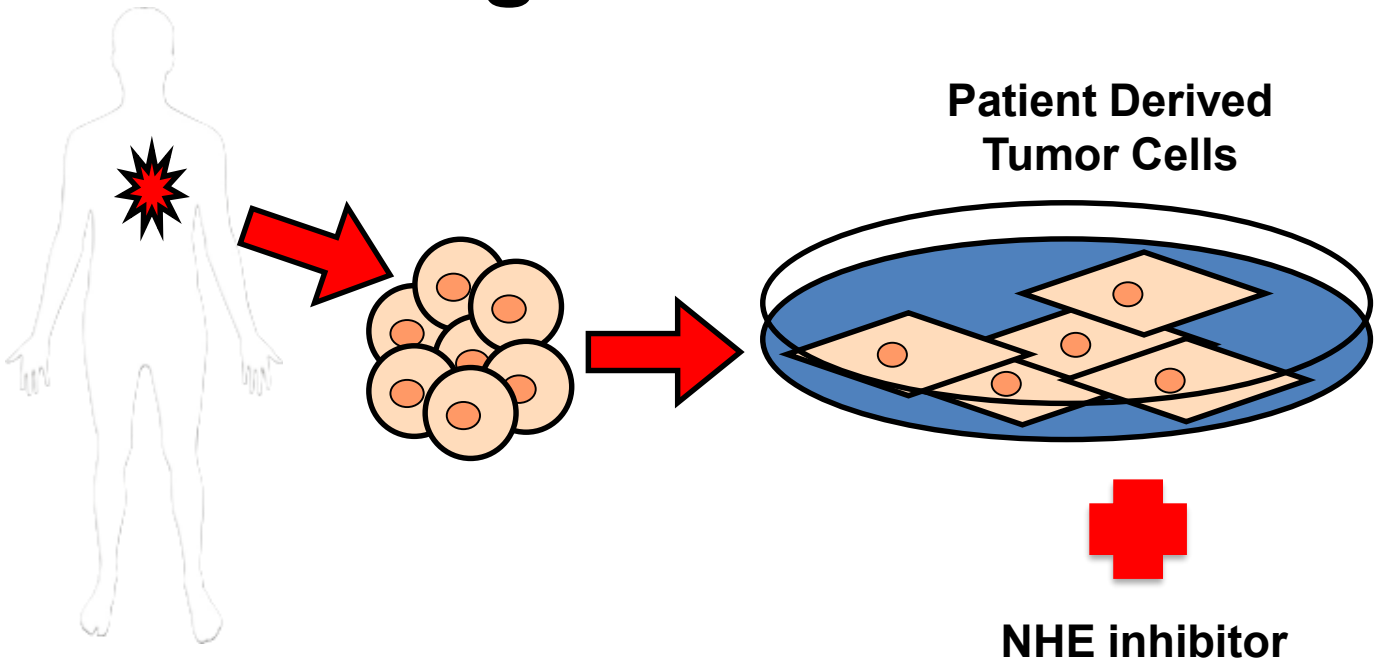
Decrease NHE expression to decrease pHi

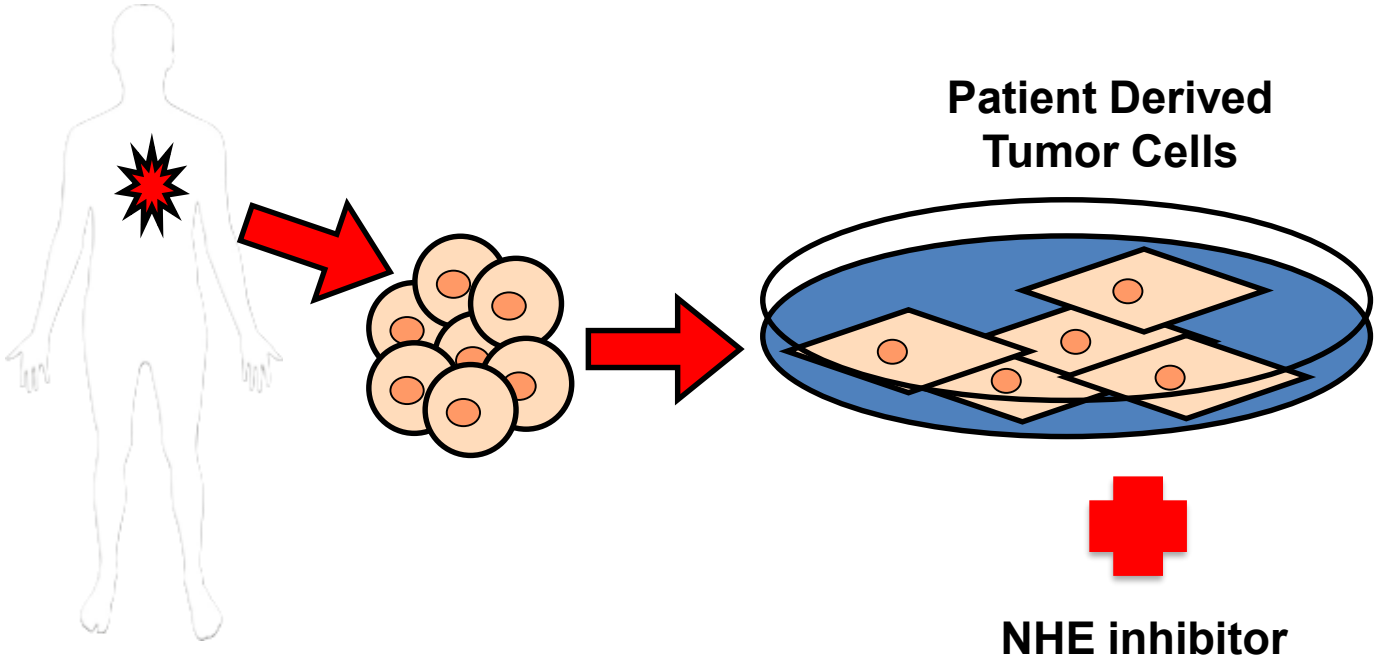
Can inhibiting NHE treat cancer?



	colon	breast
pHi Control	7.3	7.6
pHi + NHE inhibitor	7.2	7.1

Grillo-Hill, Bree K., et al. eLife 4 (2015): e03270.

NHE Inhibitors Now in Clinical Trials



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Want to learn more?

Grillo-Hill, Bree K., et al. "Increased H+ efflux is sufficient to induce dysplasia and necessary for viability with oncogene expression." *eLife* 4 (2015): e03270.

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