Tumor suppression by modulating stem cell fitness

James DeGregori
University of Colorado Denver
School of Medicine
Natural Selection can explain cancer incidence at the species level

The evolution of long-lived multicellular animals required the selection for potent tumor suppressive mechanisms.

There is minimal selection against cancer beyond the age where most animals would already be dead by other causes.

Better tumor suppression would require additional energy in early life, which would come with a cost.
Conventional View

↑ Number of oncogenic mutations → Cancer

Adaptive Oncogenesis Model

Healthy, Young → Environment Insult; Aging → 
↓ Cell Fitness, Altered Microenvironment → 
↑ Selection for adaptive mutations → Cancer

Fitness
Low

High
High stem cell pool fitness is tumor suppressive

Model for how vertebrates with large differences in somatic cell numbers and lifespans similarly avoid cancer through reproductive years.

Increased risk of somatic evolution in larger animals

- SC number/tissue: target size for oncogenic hits
- Lifespan (time available to accumulate mutations)

Decreased risk of somatic evolution in larger animals

- Is the effective population size for SCs bigger in bigger animals?
- Buffering capacity of tissue to maintain fitness
- Chance of mutation fixation by drift
- Ability of a fit stem cell pool to impede somatic cell evolution

Increased risk of somatic evolution in smaller animals

- Ability of a fit stem cell pool to impede somatic cell evolution
Why does cancer increase with age?

Accumulation of oncogenic mutations.

Changes in cellular microenvironment.

Chronic inflammation.

Decreased immune surveillance.

Does reduction of cellular fitness lead to selection for specific adaptive oncogenic mutations?
Signaling in B-progenitors Declines with Age

Henry et. al; PNAS; December 14, 2010 vol. 107 no. 50 21713-21718
Bcr-Abl Becomes Adaptive in Aged Backgrounds by Alleviating Aging-Associated Signaling Defects

Henry et. al; PNAS; December 14, 2010 vol. 107 no. 50 21713-21718
- Signaling defects in old B-progenitors contribute to reduced fitness (as determined using competitive transplantation assays.

- Bcr-Abl restores signaling, promoting selection for Bcr-Abl expression.

- Selection for Bcr-Abl within old B-progenitor pools leads to increased leukemogenesis.
What else underlies fitness defects in old B-progenitors?
Anabolic and catabolic pathways decrease in old B-progenitors
Aging is not a program

but programs can mediate aging

and aging can be deprogrammed.
Old B Cell Progenitors Exhibit Metabolic Defects

TCA Cycle Intermediates

- Citrate
- Glutamine
- Glutamate

Energy

- Adenosine
- Creatine

Lactate

- Lactate

*Rela*ve Amount

$p=0.018$  
$p=0.032$  
n.s.

$p=0.0015$  
$p=0.0034$  
$p=0.01$
ATP Levels are Decreased in Old B cell Progenitors Relative to Young Ones

**ATP Levels**

- **Young B cell Progenitors**
  - ATP Levels are higher.
- **Old B cell Progenitors**
  - ATP Levels are lower.

**Graphs**

- **Bar Graph** showing relative ATP amounts for Young and Old B cell Progenitors.
  - Young B cell Progenitors have higher ATP levels.
  - Old B cell Progenitors have lower ATP levels.
  - **p<0.0001** indicates statistical significance.

**Additional Graphs**

- **Bar Graph** showing relative ATP amounts for Myeloid Cells.
  - Young and Old Myeloid Cells have similar ATP levels.

**Chemical Reactions**

1. **Reaction 1**
   - Luciferin + ATP + Firefly Luciferase + Mg^{2+} → Adenyl-luciferin + PP_i + O_{2} → Oxy-luciferin + H_2O + CO_2

2. **Reaction 2**
   - The reaction involving ATP and oxygen leads to the formation of Oxy-luciferin, water, and carbon dioxide.
Model for Bcr-Abl Adaptation in an Aged Background

**Young B cell Progenitors**
- GLUT1
- IL-7R-pre-BCR
- glucose
  - lactate
  - glycolysis
  - AKT, STAT, etc
  - TCA → ETC → ATP

**Old B cell Progenitors**
- GLUT1
- IL-7R-pre-BCR
- glucose
  - lactate
  - glycolysis
  - AKT, STAT, etc
  - TCA → ETC → ATP
  - ↓ anabolism

**Old B cell Progenitors + Bcr-Abl**
- GLUT1
- IL-7R-pre-BCR
- glucose
  - lactate
  - glycolysis
  - AKT, STAT, etc
  - TCA → ETC → ATP
  - ↑ anabolism
  - Bcr-Abl
Aging

Accumulation of deleterious mutations → Decline in progenitor cell fitness and tissue function → Cancer

Accumulation of oncogenic mutations

B. Adaptive Oncogenesis Model

Aging

Accumulation of deleterious mutations, epigenetic changes & microenvironmental perturbations

Really?

Accumulation of oncogenic mutations → Decline in progenitor cell fitness and tissue function → Increased selection for adaptive oncogenic mutations → Cancer
Previous Irradiation (\(\text{IR}^\text{P}\))

- 2.5-5Gy
- \(\geq 2\) months

Number of \(\text{Lin}^{\text{negSca}1^+}\) Cells Day7

- \(p < 0.0001\)
- \(p = 0.0075\)
- \(p = 0.0006\)
- \(p = 0.0393\)
- \(p = 0.0087\)
Prior irradiation and HSC fitness

- Previously irradiated HSC exhibit maintenance defects that are *specific, reproducible, somatically heritable, and reversible*.

- Evolved to deal with the occasionally damaged cell?

- “Programmed Mediocrity”? 
Hmmm…. 

• Could “programmed mediocrity” be a mechanism to maintain tissue fitness in youth, but which contributes to tissue decline in old age?
So why do kids get cancer?

1) Given expansion of progenitor populations, a mutation can more easily become fixed even if not advantageous.

2) More recent evolution has substantially altered the human brain and immune systems, and a low risk of childhood leukemias affecting these tissues has been a tradeoff (although advantages of a more developed brain and better immune system outweighed the low leukemia risk).

3) There are dietary and genetic factors which correlate with reduced folate and/or reduced dNTP synthesis, which may reduce progenitor fitness, and thus may contribute to childhood cancers.

4) Our immune systems did not evolve to deal with modern conditions, but to conditions with more antigen and pathogen exposures early in life. Thus, our hematopoietic systems are not truly adapted to modern life.

5) Translocations common to childhood leukemias are more likely to occur in fetal or childhood development.