Telomerase, Stem Cells, Cancer and Aging

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Lecture: February 03, 2020 (Discussion: Feb. 25)
• Why do organisms employ stem cell hierarchies?
• Are there relationships between stem cells and cancer?
• How is telomere biology related to stem cell biology and cancer?
• How is all of this potentially related to aging?
• Do cancers use a stem cell hierarchy? ("cancer stem cells")
World record times for marathon (female)

Raw data from Association of Road Racing Statisticians
http://www.arrs.net/SA_Mara.htm
How old is he?
How old is he now?
Cancer
Uncontrolled cell division
Age-associated diseases/pathologies

- Osteoporosis
- Cataracts
- Alzheimers Disease
- COPD
- Parkinsons Disease
- Cardiovascular Diseases
- Diabetes
- Arthritis
- Cerebrovascular Disease (stroke)
- Pulmonary Fibrosis
- Chronic Liver Disease
- Sarcopenia
- Frailty
- Anemia

- Cancer
World record times for marathon (female)

Raw data from Association of Road Racing Statisticians
http://www.arrs.net/SA_Mara.htm
A woman’s risk of osteoporosis increases exponentially after menopause may be due to the reduced estrogen. Men do not show such a risk in later ages.
Cancer rates increase with age

"WHY?"

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Paul Samson, Gregory O’Grady, John Keating
Childhood cancer shows inverse of this
Epithelial Tissues
- typically actively dividing

Some examples

Others:
• Oral cavity
• Lungs
• Breast
• Liver
• Kidney
• Colon/Rectum
• Cervix
• Uterus
• Ovary
• Prostate

STEM CELLS
Both cancer and “aging” are considered by many to be “stem cell diseases”
Nothing in biology makes sense
- Cells are “Immortality”
- Divide & conquer!
- Limited by carrying capacity

Unicellular

- “Mortal”
- Specialization/co-operation
- (germ line, somatic; stem)
- Homeostasis/Self-limiting

Multicellular

evolved to

CC

CC
Uncontrolled cell division is at the heart of the cancer problem.
Number of particles in universe:

- 105 kg

Weight of the Earth in known universe!
Normal human cells have limited cell division potential.
Normal cells’ limited division potential

“Hayflick Limit” (replicative senescence)

# cell divisions are monitored

Prevents clonal overgrowth

Tumor suppressors
- P53
- pRB

Replicative Senescence – a permanent block to a cell’s ability to proliferate

(Apoptosis too)
Antagonistic Pleiotropy

Beneficial early in life but detrimental later in life
Limited somatic cell replication

(A threat in large, long-lived organisms)
“C’mon, c’mon—it’s either one or the other.”
Cellular Senescence

Several initiating triggers:

- DNA damage
- Radiation
- Activated oncogenes (oncogene induced senescence)
- Oxidative stress (stress induced senescence)
- Excess cell division (replicative senescence)

Note common theme - all potentially oncogenic!

Implies a counting mechanism: a “mitotic clock”
Telomeres

Key structural elements needed for chromosomal stability

- DNA
- PROTEINS
Human telomeres
6 protein “Shelterin” complex - telomere “capping”
Telomeres gradually shorten with age

Telomere lengths measured in Peripheral Blood Leukocytes (PBL)

$Y = 7.37 - 0.022X$

$r = -0.41, P < 0.0001$
“The terminus is the heel of Achilles of the DNA double helix...”

--A. Olovnikov, J. Theoretical Biology (1973)

End Replication Problem
- Due to mechanism of DNA replication
TELOMERASE

S.E. Artandi, New England Journal of Medicine, Sep 21 2006, 1195-1197
Normal cells have a limited division potential.

"Hayflick Limit" (replicative senescence).

Telomere maintenance prevents Rep Sen!

Cell yield during aging in a human diploid cell culture.

**Replicative Senescence**

- permanent block cell proliferation
- ALSO prevents chromosomal instability due to extreme telomere shortening
DANGER
Normal cells have a limited division potential.

"Hayflick Limit" (replicative senescence)

Cell yield during aging in a human diploid cell culture.

“Breakage-Fusion-Bridge cycles”
_Barbara McClintock (1930s)
Short, dysfunctional telomeres

Chromosome end-to-end fusions

Dicentric chromosome
Cancer cells with short telomeres exhibit anaphase bridges

Parental cells
normal anaphase

Elevated frequency of anaphase bridges in cells with short telomeres
Cancer Characteristic: Chromosomal Instability (CIN)

Prostate Cancer
Normal colon

Normal crypts 02 (40X)
Polyp w/stroma
(40X) H&E
Polyp w/stroma
(40X)

Stroma
Colon

Adenoma w/stroma (100X)
Anaphase bridging
In adenomatous polyp
With shorty telomeres
Cell Division

Average Telomere Length (kb)

Model for role of telomere loss in tumorigenesis

Telomere stabilization

"Immortalized"

(p53, pRB)
Stem Cells/Cancer Stem Cells
Unicellular

SOMATIC CELLS

Multicellular

GERM CELLS
**Germ-line**

- Immortal (required!)
- Telomerase (+++)

**Somatic cells**

- Mortal
- Telomerase (-)

**Stem cells**

- Compromise
- Repair
- Replacement

**Telomerase (+)**

- Allows for extra cell division capacity

“DISPOSABLE SOMA THEORY”

_Thomas Kirkwood_
Telomere length

Differentiated somatic cells

Germ cells

Cell division (age)

Stem cells

SENESCENCE

CHROMOSOME INSTABILITY
Figure 12-1 The Biology of Cancer (© Garland Science 2007)
Ki67 protein
Proliferation biomarker

Diagram of an individual colon crypt showing the position of the different cell types including stem cells at the base of the crypt.
Why use stem cell-driven hierarchical structure?

• Cell division is risky (mutations)
  – Long-lived organisms
  – Need for tissue repair and maintenance
    • Rapidly proliferating tissues

• Use of a TA compartment allows for infrequent stem cell division

• Protected location (stem cell niche)

• More robust maintenance mechanisms in stem cells
Stem cell divisions & cancer

Tomasetti and Vogelstein, Science Jan. 2015
How does telomere biology impact stem cell function?

- Stem cells have telomerase activity (but low levels)
- Inherited mutations leading to telomere shortening cause diseases due to compromised stem cell function (depletion, lowered replicative potential)
- Accumulation of senescent stem cells may impact aging

- Studies in mice engineered to eliminate senescent cells reduce age-related pathologies
Cancer stem cells

• Why invoke?

1. Stem cells traditionally thought likely targets for malignant transformation
2. Tumors are heterogeneous and cells variably express differentiated markers – “Caricatures of normal tissue” - B. Pierce
3. Tumors are clonal
4. Cancer common in tissues with stem
5. Most cancers are telomerase-positive
Hematopoietic reconstitution assay (bone marrow stem cells)

Lethally irradiated host

Inject bone marrow cells from healthy donor

HSC colonize recipient marrow, reconstitute blood cells
Cancer stem cells?

Cell subpopulations isolated by antibody binding to cell surface markers.

NO CANCER

NO CANCER

NO CANCER

CANCER
Cancer stem cells?
Cancer stem cell concept

1960s-1970s
- Mouse cancers (leukemias, teratocarcinomas)
- **Only a SUBSET** of the cancer cells could initiate a new tumor

Later done with other tumor types (e.g. breast, brain tumors)
Possible properties of cancer stem cells

Shared with normal Stem cell
- Rare(?)
- Self-renew
- Telomerase positive ("immortal"????)
- Express "stemness" genes (Oct4, Nanog, Sox-2, etc.)
- Multipotent (can reform original heterogeneous tumor)

CSC-specific
- Tumorigenic
- Source of metastatic spread to other organs
- Contribute to treatment-resistance and/or disease relapse
- Unique niche???
Possible Origins of cancer stem cells?

- **NSC** is often presumed to be the source
  - long-lived, multipotent, immortal, self-renew

- **TA** population
  - may share many stem cell attributes
  - highly proliferative
  - highly abundant (larger target)

**BOTH** sources have been clearly demonstrated in human leukemias
Are there different degrees of “stemness”??
Clinical Implications of the CSC concept

1. Current therapies focused on the tumor bulk may leave behind CSC
2. Remaining CSC may underlie relapse and metastatic spread
3. Current assessment of anticancer drugs are based on substantial responses (e.g. Tumor shrinkage)
Implications of the CSC concept (cont’d)

4. Could provide novel targets for treatment (e.g. self-renewal, niche signals) but will need to be CSC-specific!

5. Stem cell properties may need to be considered when designing new therapies (e.g. chemo- and radio-resistance of CSC)
Potential therapeutic approaches targeting CSC

1. Eliminate self-renewal
2. Induce differentiation
3. Inhibit drug transporters (e.g. efflux pumps)
4. Antagonize the CSC niche
5. Exploit other diffs. Betw/ CSC and NSC

Possible side-effects in NSC

...but, some tissues are not essential!
(breast, prostate, etc.)
Summary: Cancer’s strong age-association

1. Mutations accumulate w/age
   ✓ Unrepaired DNA replication errors (cell division link)
   ✓ Unrepaired DNA damage
Summary: Cancer’s strong age-association

2. Evolved anti-cancer mechanisms

Cellular Replicative Senescence
- Limits clonal expansion

Stem Cell hierarchical tissue organization
- Limits proliferation to cell subset
Summary: Cancer stem cells

3. Cancer may be the result of eventual breakdown of protective anti-cancer mechanisms over time; linked to our unnaturally long lives in the modern era.

- Loss of functional Senescence program
- Accumulation of mutations and/or critical telomere shortening in long-lived Stem Cells

✓ Antagonistic pleiotropy
  _Promotes cancer in older people
  _Promotes “Aging” pathologies
Summary: Cancer stem cells

4. Cancer stem cells have been identified in some cancers
   ✓ How many other cancers is debatable
   ✓ Origin(s) of CSC uncertain
   ✓ CSC may underlie cancer relapse/therapeutic resistance