Aging and Cancer: Rival Demons?
Aging and Cancer are Biological Linked

Understanding Aging is Key to Understanding Cancer
Cancer is linked to aging

What is cancer?

What causes cancer?

What limits cancer?

How are cancer and aging linked?
Cancer Rises Exponentially with Age

Age is the largest single risk factor
Incidence vs mortality
Similar to other age-related diseases
Cancer Incidence Scales with Life Span

Mice and Humans are ~ 97% Genetically Similar
Postponed Aging Delays Cancer

Mice

"Restricted" Diet

"Normal" Diet

% ALIVE

0%

100%

CANCER INCIDENCE

AGE

1 2 3 4
The RATE at which cancer increases is proportional to the RATE of aging.
Cancer is linked to aging

What is cancer?

What causes cancer?

What limits cancer?

How are cancer and aging linked?
Cancer is an abnormal mass (tumor), resulting from cell proliferation, that has the potential to kill the organism.

Cancer is much more than cell proliferation.
CANCER ARISES FROM RENEWABLE TISSUES
Composition of Complex Organisms

CELLS

EXTRACELLULAR MATERIAL

POST-MITOTIC
(non-renewable)

MITOTIC
(renewable)

Degenerative disease

Degenerative disease
Cancer
Five Characteristics of Malignant Cells

Loss of growth control, including avoidance of senescence (neoplasia) *

Avoidance of cell death (apoptosis resistance) *

Stimulation of blood vessel formation (angiogenesis)

Invasion into surrounding tissue (invasion)

Ability to colonize distal tissues (metastasis)
Loss of growth control (neoplasia)

Inappropriate cell division

Unlimited cell division potential (cellular senescence; replicative immortality)

Activation of growth promoting genes [oncogenes]

Inactivation of growth inhibitory genes [tumor suppressor genes]
Avoidance of Apoptosis  
*(cell death)*

Resistance to physiological  
"death" signals

Resistance to damage-induced  
death signals  
*(survival of cells with genomic instability)*

Activation of growth promoting genes  
*[oncogenes]*

Inactivation of growth inhibitory genes  
*[tumor suppressor genes]*
Cancer is linked to aging

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How are cancer and aging linked?
Cancer cells acquire malignant properties through de novo somatic mutations (activation of oncogenes or inactivation of tumor suppressor genes)
Cancer cells also require a tissue microenvironment that permits the growth and survival of mutant cells (disruption of normal tissue structure and function).
Mutations accumulate throughout life
Potentially oncogenic mutations are present even in young apparently normal tissues

Tissue structure changes throughout life
Young tissues are often structurally distinguishable from middle-aged and old tissues

If mutations and tissue structure change throughout life, why then do we not get cancer more often?
Cancer is linked to aging

What is cancer?

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How are cancer and aging linked?
Evolution of Long-Lived, Complex Organisms

**LIFE SPAN**

- Single-celled: Min/hrs
- Multi-cellular, Post-mitotic: Days/wks
- Multi-cellular, Post-mitotic + Renewable tissues: Years

**ORGANISMS**

**CELL DIVISION IS RISKY!!**
Risky business of CELL DIVISION

3 billion bp DNA:

- Unpackaged (loss of protection)
- Replicated (fidelity; repair)

Mutation Fixation
Organisms with renewable tissues had to evolve mechanisms to prevent cancer

*Tumor Suppressor Genes*
Two Classes of Tumor Suppressor Genes

• **CARETAKERS -- act on the genome**
  Damage prevention and repair

• **GATEKEEPERS -- act on cells**
  Apoptosis - eliminates potential cancer cells
  Cellular senescence - prevents their growth
**Apoptosis Suppresses Cancer**

- Cancer cells frequently acquire mutations that inhibit cells from sensing or processing physiological death signals.

- Mutations that dampen the apoptotic response greatly increases susceptibility to cancer.

- Apoptosis is controlled by the two most powerful tumor suppressor pathways (p53 and pRB).
Cellular Senescence Suppresses Cancer

• Cancer cells frequently acquire mutations that abrogate the senescence response

• Mutations that dampen the senescence response greatly increases susceptibility to cancer

• Cellular senescence is controlled by the two most powerful tumor suppressor pathways (p53 and pRB)
Caretaker tumor suppressor genes are longevity assurance genes.

Gatekeeper tumor suppressor genes can be antagonistically pleiotropic.
Aging before cell phones ........

"Hazardous" Environment (climate, predators, infection, etc)

"Protected" Environment (climate control, biomedical intervention etc)
Mutation Accumulation ("bad" genes can persist)

Antagonistic Pleiotropy
(what’s good for you when you’re young can be bad for you when you’re old)
Why might gatekeeper tumor suppressors -- be antagonistically pleiotropic??

**APOPTOSIS** -- culls defective cells..... but deplete tissues of cells

**CELLULAR SENESCENCE** -- arrests proliferation of defective cells ..... but senescent cells are dysfunctional
Testing the hypothesis that gatekeeper tumor suppressors are antagonistically pleiotropic:

Cellular senescence
Cellular Senescence: Arrests Cell Proliferation In response to Potential Cancer-Causing Events

Irreversible arrest of cell proliferation

- Short/dysfunctional telomeres (REPLICATIVE SENESCEENCE)
- DNA Damage
- Chromatin Instability
- Supraphysiological Mitogenic/ Stress Signals
- Oncogenes
The Senescent Phenotype is Not Simply an Arrest of Cell Proliferation

- Irreversible Growth Arrest
- Resistance to Apoptosis
- Altered Function/Gene Expression
The senescent phenotype:  
Altered pattern of gene expression

Cell cycle regulation

Cell structure

Metabolism

Biologically active secreted molecules

Proteinases

Cytokines

Growth factors
Secreted molecules upregulated by the senescence response

**Proteinases/regulators**
- MMP-1
- MMP-3
- Elastase
- TIMP-2
- PAI-1

**Growth Factors/regulators**
- EGF
- Heregulin
- IGFBP-3
- IGFBP-4

**Cytokines**
- TGF-β
- IL-1
- IL-6
- GRO(KC)
- MIP-1

- Alter tissue structure
- Alter cell proliferation
- Alter cell motility, inflammation
OLD TISSUE

EPITHELIUM
Basement Membrane

STROMA

Degradeative & inflammatory molecules, growth factors, etc

Senescent Fibroblast

Neoplastic Growth

"Initiated" Cell

SELENESCENT Epithelial Cell

AGING?
Testing the hypothesis that cellular senescence is antagonistically pleiotropic

Do senescent cells exist and accumulate with age in vivo?

Goberdhan Dimri

Senescent Cells Accumulate In Vivo

With Increasing Age
Skin
Retina
Liver
Spleen

At Sites of Age-Related Pathology
Venous ulcers
Atherosclerotic plaques
Benign prostatic hyperplasia
Preneoplastic hepatic lesions
Testing the hypothesis that cellular senescence is antagonistically pleiotropic

Do gatekeeper tumor suppressor genes accelerate aging?

Larry Donehower
Heide Scrable


p53 - a quintessential gatekeeper tumor suppressor gene

Transcription factor
(activation and repression of multiple target genes)

Binds DNA as a tetramer
(Donehower/Scrabble mutant/short forms thought to assemble mixed tetramers)

Mixed tetramers “hyperactive”
(hyper-transcriptional activation and/or repression, or altered spectrum of target genes)
“Hyperactive” p53

**Donehower mouse**: cancer-free but prematurely aged!

*Enhanced apoptotic response to damage*  
(published)  
*More senescent cells in tissues of mutant mice*  
(unpublished)

**Scrabble mouse**: small size, cancer-free but prematurely aged!

*Enhanced senescence owing to supraphysiological IGF-1 signaling*  
(unpublished)
Hyperactive p53

Altered p53-dependent gene expression

- ↑ p21
  - Cell Cycle Arrest

- ↑ IGF-1 signaling
  - Sustained ERK
    - Senescence
      - Small Size, Tumor Suppression
      - AGING
Testing the hypothesis that cellular senescence is antagonistically pleiotropic

Do senescent cells facilitate age-related pathology?
(CANCER)

Ana Krtolica
Simona Parrinello

Krtolica A, Parrinello S, Lockett S, Desprez P, Campisi J
**Senescent Fibroblasts Stimulate the Proliferation of Premalignant Epithelial Cells**

<table>
<thead>
<tr>
<th>Human Fibroblasts (WI-38)</th>
<th>HaCAT Human Keratinocytes</th>
<th>SCp2 Mouse Mammary</th>
<th>S1 Human Mammary</th>
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<tbody>
<tr>
<td>Presenescence</td>
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<tr>
<td>Senescent</td>
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</tbody>
</table>

![Images of cell cultures](image-url)
Senescent Fibroblasts Stimulate Tumorigenesis of Premalignant Epithelial Cells In Vivo

- SCp2 cells alone
- + Presenescent Fibroblasts
- + Senescent Fibroblasts

Tumor size (mm³ x 10)

Days
Testing the hypothesis that cellular senescence is antagonistically pleiotropic

Do senescent cells disrupt normal tissue function?

Simona Parrinello
Ana Krtolica
Jean-Philippe Coppe
Three dimensional cultures to study tissue structure and function:

Human and mouse mammary epithelial cells organize into physiological alveoli when cultured with appropriate components in 3D

Morphological organization
Functional differentiation
Senescent fibroblasts inhibit morphological and functional differentiation

BM + PreS Fb  BM + Sen Fb

β-casein  DAPI

Pre-S Fb  Sen Fb

β-casein

E-cadherin
Senescent fibroblasts derange mammary morphogenesis

Presenescent fibroblasts

Senescent fibroblasts

Core Area Number

PRIMAR Y S EC ONDA RY T ER T IA R Y
Cellular senescence, a tumor suppressor mechanism, prevents cancer early in life.

Late in life, accumulation of senescent cells can disrupt normal tissue structure and function.

Accumulated senescent cells may synergize with accumulated mutations to promote cancer and age-related tissue dysfunction.
Can senescent phenotypes be reversed?

Christian Beausejour, Ana Krtolica, Francesco Galimi, Masashi Narita, Scott Lowe, Paul Yaswen

Lentiviruses ---> high-efficiency expression of genes in senescent cells

**Lenti-GSE** (inactivates p53)

**Lenti-CDK4m** (inactivates pRB)

**Lenti-p16** (activates pRB)

**Lenti-p16(RNAi)** (inactivates pRB)
Replicatively Senescent
WI-38
(fetal lung fb)

+ Lenti-GSE (inactivate p53)

No proliferation

Replicatively Senescent
BJ
(foreskin fb)

20 Doublings
On the horizon ......

• Molecular strategies to eliminate (or reverse the phenotype of) senescent cells

• Cell based therapies (stem cells) to replace senescent cells or cells lost through apoptosis in degenerated tissues
Aging and Tumor Suppression

Can tumor suppression and aging be uncoupled??
Jean Philippe Coppe
Joshua Goldstein
Ana Krtolica
Francis Rodier
Simona Parinello

Christian Beausejour - Sangamo
Pierre Desprez - CPMC
Goberdhan Dimri - NW U

Francesco Galimi/Inder Verma - Salk
Steve Lockett - LBNL/NCI
Masa Narita/Scott Lowe - CSH
Enrique Samper/Simon Melov - Buck
Carlos Ortiz de Solorano - LBNL
Paul Yaswen - LBNL