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

"Normal" Diet

"Restricted" Diet

% ALIVE

CANCER INCIDENCE

AGE

0%

100%
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

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  
(\textit{cell death})

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

- Activation of growth promoting genes  
  [\textit{o}ncogenes]
- Inactivation of growth inhibitory genes  
  [\textit{t}umor suppressor genes]
Cancer is linked to aging

What is cancer?

What causes cancer?

What limits cancer?

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?

What causes cancer?

What limits cancer?

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

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

Organisms

- Cancer

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 ..........

100% SURVIVORS

AGING

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

"Protected" Environment (climate control, biomedical intervention etc)
SURVIVORS

AGE

"Natural" Environment
(hazards, 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
- DNA Damage
- Supraphysiological Mitogenic/Stress Signals
- Oncogenes
- Chromatin Instability
- Short/dysfunctional telomeres (REPLICATIVE SENESCEENCE)
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

<table>
<thead>
<tr>
<th>Proteinases/regulators</th>
<th>Growth Factors/regulators</th>
<th>Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-1</td>
<td>EGF</td>
<td>TGF-β</td>
</tr>
<tr>
<td>MMP-3</td>
<td>Heregulin</td>
<td>IL-1</td>
</tr>
<tr>
<td>Elastase</td>
<td>IGFBP-3</td>
<td>IL-6</td>
</tr>
<tr>
<td>TIMP-2</td>
<td>IGFBP-4</td>
<td>GRO(KC)</td>
</tr>
<tr>
<td>PAI-1</td>
<td></td>
<td>MIP-1</td>
</tr>
</tbody>
</table>

- Alter tissue structure
- Alter cell proliferation
- Alter cell motility, inflammation
EPITHELIUM
Basement Membrane

STROMA

YOUNG TISSUE

"Initiated" Cell

OLDER TISSUE

Senescent Epithelial Cell

Neoplastic Growth

Degradative & inflammatory molecules, growth factors, etc

Senescent Fibroblast
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/Scrable 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

IGF-1 signaling

Sustained ERK

Cell Cycle Arrest

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

- HaCAT Human Keratinocytes
- SCp2 Mouse Mammary
- S1 Human Mammary

Human Fibroblasts (WI-38)

Presenescent

Senescent
Senescent Fibroblasts Stimulate Tumorigenesis of Premalignant Epithelial Cells In Vivo

SCp2 cells alone

+ Presenescent Fibroblasts

+ Senescent Fibroblasts

Tumor size (mm$^3 \times 10$)

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
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)

---

**Diagram**

- **ARF**
  - **MDM2**
    - **p53**
  - **p16**
    - **CDK4**
      - **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

Aging Phenotypes

Gatekeeper
Tumor Suppressors

Cancer

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