What IS Aging?

Aging is a process that changes a fit (young) organism into a less fit (old) organism.
Age-related diseases rise exponentially with age.

Age is the largest single risk factor.
Aging = susceptibility to disease

AGE

CANCER

HEART FAILURE

STROKE

DEMENTIA

MULTI-SYSTEM DECLINE

BASIC AGING PROCESS
What are the basic aging process that link aging and age-related disease?

What does aging and any basic aging process have to do with retroviruses and opportunistic infections?
Medicine has made remarkable progress in treating two important diseases:

- childhood/young adult cancer
- HIV/AIDS

These triumphs have a cost:

- age-related pathologies that appear years after treatment
Age-related diseases are (mostly) degenerative

- Neurodegeneration, cognitive loss
- Sarcopenia, frailty
- Heart disease
- Macular degeneration
- Vascular disease
- Osteoporosis
- Decreased Liver, kidney function
- Diabetes
- CANCER
Is there a common biology that links cancer, degenerative disease and aging?

(a working hypothesis .... and model)
What causes aging?

**Damage and damage responses**

- Evolutionary antagonistic pleiotropy
- Epigenetic drift
- Genotoxic stress
- Germline mutation accumulation
- Somatic mutations
- Telomere dysfunction
- Cellular senescence
-Mitochondrial dysfunction
Suppressing cancer costs -- aging

Tumor Suppressor mechanisms

Aging Phenotypes

Late life phenotypes, including cancer (antagonistic pleiotropy)

Care-takers
prevent/repair DNA damage, mutations

Gate-keepers
eliminate/arrest damaged/mutant cells

Apoptosis
Deplete proliferating/stem cell pools ---> Tissue atrophy/degeneration

Senescence
Deplete proliferating/stem pools
Cell dysfunction ---> loss of tissue function/homeostasis

Longevity assurance
What is cellular senescence?

Mitotically competent cell → post-mitotic

Induced by many potential cancer-causing stresses

Senescent remain viable, metabolically active, and do not die
When and where are senescent cells in vivo?

At Sites of Age-Related Pathology
Venous ulcers, atherosclerotic plaques, arthritic joints, COPD, visceral fat, AD brain, etc
Benign prostatic hyperplasia, pre-neoplastic lesions

Dimri et al., PNAS, 1995
Noureddine et al., Circulation, 2011
What defines a senescent cell?

- Persistent DNA damage foci (DNA-SCARS/TIF)
- Heterochromatin foci (SAHF)
- p16INK4a loss/secretion
- SA-Bgal
- lamin B1 loss
- HMGB1 loss

GROWTH | ARREST

SASP
Causes of cellular senescence

- Genotoxic stress (anti-cancer therapies)
- Mitochondrial stress (anti-retroviral therapies)

Cellular Senescence (tumor suppressive)

- Growth arrest
- SASP (inflammation)
Chemotherapy induces a SASP in human cells in vivo: PROSTATE CANCER EPITHELIAL CELLS

Senescence markers

Proliferation markers

Gene expression in patients' prostate before and after chemotherapy

SASP components
Inflammation causes or contributes to virtually every major age-related pathology, including cancer. Aged tissues are inflamed: “sterile” inflammation. The SASP is pro-inflammatory.
High Mobility Group Box 1 Protein (HMGB1)

HMGB1 re-localization in Aging Mice

Davalos et al., J Cell Biology:201 2013
Irradiation-Induced senescence promotes loss of nuclear HMGB1

Davalos et al., J Cell Biology:201 2013
Remaining Intracellular HMGB1 necessary for SASP

Davalos et al., J Cell Biology: 201 2013
Extracellular HMGB1 promotes Senescence

% SA-β-Gal Positive

- BSA
- HMGB1
- HMGB1 + HM
- HMGB1 + IgG

Cell Number

- IMR90 BSA
- IMR90 HMGB1
HMGB1 levels increase in serum from older individuals

**Graph**

- **Y-axis**: HMGB1 ng/ml
- **X-axis**: AGE
- **Data Points**
  - Age range 19-22
    - HMGB1 levels: 0 ng/ml
  - Age range 72-89
    - HMGB1 levels: 28 ng/ml

**Statistical Significance**

- p-value: <0.03
- **Significance Level**
  - ***: Highly significant
ART ineffective in reducing senescence secretion

**Graphs:**

- **HMG1B ng/ml**
  - HIV-
  - HIV +
  - HIV ART

- **IL-6 pg/ml**
  - HIV-
  - HIV +
  - HIV ART

Statistical significance:

- HMG1B: ***<0.04***
- IL-6: ***<0.01***
Kaposi Sarcoma Patients exhibit reduced HMBG1
DAMAGE

p53

SASP

AGING,
LATE-LIFE CANCER

Cell autonomous
tumor suppression

Cell non-
autonomous
tumor suppression

HMGB1

p53

SASP

AGING,
LATE-LIFE CANCER

Cell autonomous
tumor suppression

Cell non-
autonomous
tumor suppression

?
Acute inflammation, such as that caused by acute infection, produces toxic damaging molecules that can result in long-term persistent DNA damage.

Greatest sources of somatic damage are the reactive oxygen species (ROS) that are byproducts of normal mitochondrial metabolism.
Many anti-retroviral nucleoside analogues inhibit the polymerase that replicates mitochondrial DNA.

In addition, viral load fuels inflammation, which can damage tissues via immune-dependent and immune-independent mechanisms.
**Inhibit mtDNA polymerase**

Acute Infection

- Reduce functional mtDNA
- Reduce mito ETC function
- Increase intracellular ROS

Damage DNA, RNA, protein, lipid, etc

**REPAIR**

(accurate)

(inaccurate = mutations)

**DIE**

(necrosis)

(apoptosis)

(tissue atrophy)

**SENUESCE**

(compromise renewal)

(inflammation)
Inflammation: causes or promotes most, if not all, age-related diseases, including cancer
Senescent cells ....

Present at the right time and place to drive aging and many age-related diseases
Why might senescent cells drive age-related pathology?

*SASP = senescence-associated secretory phenotype

HMGB1
loss/
secretion

SASP*

*Inflammation
Clearing Senescent Cells in Mice

Prematurely aged mice:
cataracts, sarcopenia, osteoporosis, fat loss, cardiomyopathy

*senescent cells accumulate*

*senescent cells eliminated*

Senescent cells can be eliminated from naturally aged mice

Luminescence and GCV treatment in aging p16-3MR mice

parallel age-related increase in endogenous p16INK4a, 3MR, IL-6

Demaria et al, submitted
Why do organisms develop a senescence/SASP response?
SASP components can facilitate tissue repair

Embryonic Development promotes tissue regeneration

Deleterious effects result from chronic SASP activity

Does the SASP entail mechanisms to prevent chronic activity?
LEUKOCYTES KILL SENESCENT CELLS

Jean-Philippe Coppe and Steve Yannone
(unpublished data)
Which immune cell types are responsible for killing senescent cells?

A role for natural killer (NK) cells
STRESSED/DAMAGED CELLS

Natural killer cell recognize stressed/damaged cells via cell surface receptors and ligands.
Senescent cells express NK ligands

Jean-Philippe Coppe and Steve Yannone (unpublished data)
Killing of senescent cells is (partially) NKG2D-dependent

Jean-Philippe Coppe and Steve Yannone (unpublished data)
Senescent cells 'identify' themselves as damaged/dysfunctional

GOOD NEWS!
The innate immune system can detect and destroy senescent cells!

BAD NEWS!
Some persist, creating sites of local inflammation.

WHY?
MMPs can cleave cell surface ligands, creating 'decoys' in the tissue microenvironment.
Senescent cells secrete MMPs, which can cleave cell surface bound receptors and ligands.

Jean-Philippe Coppe and Steve Yannone (unpublished data)
MMP-dependent evasion of killing

MICA SURFACE IMMUNOSTAINING

DAY 9

DAY 9 + MMPi

DAY:

100%

% living cells

1 4 7 10

1 4 7 10

1 4 7 10

SEN alone + leukocytes + leukocytes + leukocytes + leukocytes

+ NKG2D inhibitor + MMP inhibitor

Jean-Philippe Coppe and Steve Yannone (unpublished data)
Anti-retrovirals
  - Mito inefficiency
    - Increase ROS (chronic)
      - Damage (DNA)
        - Cellular senescence
          - Chronic inflammation
            - Age-related disease

Infection
  - Acute inflammation
THANKS!

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