Biological and clinical aspects of research in cancer and aging

Lodovico Balducci
H. Lee Moffitt Cancer Center
Tampa, Florida
Cancer and aging: the extent of the problem

Yancik et al, Semin Oncol, 2004
The crossroads of cancer and aging

- Cellular senescence and carcinogenesis
- Stromal senescence, carcinogenesis and tumor growth
Definition of aging

- Loss of homeostasis
- Loss of entropy and fractality
Definition of a fractal

A unity subdividing into unities of the same type, whose number and length is unpredictable.
Biological fractals
Fractality loss

- Cell loss.
- Cell damage $\rightarrow$ Functional loss $\rightarrow$ Cancer
- Stromal changes: loss of homing capacity, for stem cells.
- Loss of vessels
- Increased acellular stroma (fibrous tissue).
Metabolism of aging

- Reactive Oxigen Species (ROS) $\rightarrow$ Genomic Damage
- Advanced Glycation End Products (AGEs) $\rightarrow$ Stromal damage
- Chronic Inflammation $\rightarrow$ ROS et AGEs
- Telomere shortening
Genomic damage

- DNA hypomethylation et hypermethylation
- Histone Dehacetylation
- Micro-RNA
- DNA adducts
- Genetic Instability
Campingi, 2008

Diagram:

- **Macromolecular damage**
  - Spontaneous errors
  - (epi)genomic drift
  - Cellular responses (apoptosis, senescence, etc)
  - Tissue atrophy, loss of regenerative capacity
  - Programmed
  - Tissue/organ functional decline, degenerative or hyperplastic disease

- **Dysfunctional genes, proteins**
  - Altered regulatory circuits
  - Stochastic
Why is cancer more common in older individuals

- Duration of carcinogenesis
- Increased susceptibility of aging cells to environmental carcinogens
- Changes in body environment that favor cancer development and cancer growth
Crossroads of cancer and aging: duration of carcinogenesis

carcinogens

↓

cancer
Cancer of the lung

Changes in mortality related to lung cancer, ACS, 2002
Crossroads of cancer and aging: susceptibility of older tissues to late-stage carcinogens

Same dose of carcinogen
Links of aging and cancer in humans

- Geometric increment of the incidence of cancer of the colon and prostate with aging
- Increase rate of transformation of intestinal polyps with aging
- Epidemics of lymphomas and cerebral tumors
- Age as a risk factor for MDS and Acute leukemia after chemotherapy and radiotherapy
- Inverse relationship between telomere length and cancer risk
- Trieste, Italy: the incidence of lung cancer for the same dose of pollutant increased with age
## Rate of transformation of colonic polyps with age

<table>
<thead>
<tr>
<th></th>
<th>55-59</th>
<th>80+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>2.67</td>
<td>5.1</td>
</tr>
<tr>
<td>Women</td>
<td>2.6</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Brenner et al, 2007
## Lunghezza dei telomeri e incidenza del cancro

<table>
<thead>
<tr>
<th></th>
<th>Telomeri piu’ lunghi</th>
<th>Telomeri di lunghezza intermedia.</th>
<th>Telomeri piu’ corti</th>
</tr>
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<tbody>
<tr>
<td><strong>Incidenza annuale</strong></td>
<td>5.1</td>
<td>14.2</td>
<td>22.5</td>
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<tr>
<td><strong>Rischio relativo</strong></td>
<td>1.0</td>
<td>2.15</td>
<td>3.11</td>
</tr>
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</table>
GERIATRIC ONCOLOGY: CANCER EPIDEMICS AMONG THE AGED
Anti-proliferative genes

- Caretakers (repair of DNA damage)
- Gatekeepers (control of the proliferative gate)
Proliferative senescence of stem cells and cancer
Cellular senescence and cancer
Micro-environmental changes that may cause an increased incidence of cancer

- Chronic and progressive inflammation → local carcinogens + DNA damage + angiogenesis.

- Proliferative senescence of fibroblasts → reduction of apoptosis, increased production of tumor growth factors and lytic enzymes

- Proliferative senescence of lymphocytes → immune-senescence and inflammation.

- Endocrine senescence → increased insulin resistance → increased concentration of C peptide and I-GF1

- Obesity → increases concentration of Adiponectin
Figure 2. Age regression coefficients and their 95% CIs estimated from linear models predicting level of inflammatory markers

Proliferative senescence of fibroblasts

- Resistance to apoptosis
- Metalloproteinase
- VEGF
- heregulin

Senescent fibroblast
Senescence associated secretory phenotype (SASP)

A. Comparison between the SASPs of normal epithelial cells (P/E) and normal fibroblasts, after XRA-induced senescence.

<table>
<thead>
<tr>
<th>Secretory Profile</th>
<th>Fibroblasts (FIB)</th>
<th>Epithelial (EPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>GRO-alpha</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>GRO</td>
<td>0.00</td>
<td>0.04</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>uPAR</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>TIMP-2</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>ICA-M-1</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>ENA-78</td>
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</tr>
<tr>
<td>Osteoprotegerin</td>
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</tr>
<tr>
<td>MCP-1</td>
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<td>0.00</td>
</tr>
<tr>
<td>IGFBP-2</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>PIGF</td>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>sTNF RI</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>HGF</td>
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<td>IL-6 R</td>
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<td>CCL-28</td>
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<td>Amphiregulin</td>
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<td>HCC-4</td>
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<tr>
<td>VEGF</td>
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<tr>
<td>GCP-2</td>
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<tr>
<td>IL-1 R4/GT2</td>
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<tr>
<td>IL-1-beta</td>
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<td>IL-11</td>
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<tr>
<td>IL-1-alpha</td>
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</tr>
<tr>
<td>Fas/ TNEFPR76</td>
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<td>Osteopontin</td>
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<tr>
<td>Axl</td>
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<td>0.00</td>
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<tr>
<td>UF1G</td>
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<td>Acrp30</td>
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<tr>
<td>ICA-M-1</td>
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<td>0.00</td>
</tr>
<tr>
<td>BTC</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>IGFBP-2</td>
<td>0.04</td>
<td>0.02</td>
</tr>
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</table>

B. Trend comparison between the secreted factors of normal epithelial cells (P/E) and normal fibroblasts, after XRA-induced senescence.

- co-regulated factors
- not co-regulated factors (opposite trend)

C. Comparisons of growth status and cell status of epithelial cells.

<table>
<thead>
<tr>
<th>Growth status</th>
<th>Cell status</th>
<th>Epithelial cell strain or line</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEN (XRA)</td>
<td>normal</td>
<td>P/E</td>
</tr>
<tr>
<td></td>
<td>immortalized</td>
<td>BPH1, RWPE1, PC3</td>
</tr>
<tr>
<td>PRE</td>
<td>normal</td>
<td>P/E</td>
</tr>
<tr>
<td></td>
<td>immortalized</td>
<td>BPH1, RWPE1, PC3</td>
</tr>
</tbody>
</table>

Number of samples:
- IL-6: 3
- uPAR: 4
- TIMP-2: 3
- GRO: 4
- ENA-78: 4
- ICA-M-1: 6
- BTC: 2
Cancer and cellular senescence

IGF
Growth factors, insulin

IGF-IR

PI3 kinase

PI3

PTEN

AKT

AMPK

FOXO

TOR

Translation

p53

Genotoxic stress

Cell cycle arrest
Cellular senescence

BCL2

BAX

Apoptosis

Mitochondria and mitochondrial respiratory chain

Apoptosis
Antioxidant defence
Gluconeogenesis

FOXO

SIR proteins

Cell fate, stress resistance, metabolic functions

Cell survival
Fat mobilization
Gluconeogenesis

Campisi, 2008
The genes of aging

- Stress induced senescence results in SASP, and this phenotype is amplified by k-ras
- FOX(P3) is essential to T cell sensitization and is downregulated in cancer patients and in the elderly
- Tumor in elderly patients (colon and breast) have increased expression of genes modulating inflammation and immune response
Sénescence cellulaire et cancer
General conclusions and contradictions

- Reduced formation of ROS is associated with a prolongation of life expectancy. Exception the African mole that has a life span of 25 years, though it produces as many ROS as the common mice.

- Reduced proliferation is associated with a reduction of cancer risk. Proliferative senescence of fibroblasts and of lymphocytes may increase the risk of cancer.

- Reduced concentration of insulin and IGF-1 is associated with reduced risk of cancer.

- Inflammation may be a risk factor for carcinogenesis and cancer growth.
Research questions

- Can we increase a population life-expectancy?
- Can we increase a population life span?
- Can we reduce the risk of cancer while increasing life-expectancy and life-span?
Definitions

- **Life expectancy**: the average number of years a population cohort is expected to live from a prefixed time.
- **Life span**: the number of years we are programmed to live.
Can we increase the life-span of a species?

Yes for

- Nematodes
- Flies
- Mice
Life-span and cancer risk

- Transgenic mice with a mutated P53 have a reduction of both life-span and cancer
- Mice with a duplication of P53 WT had a normal life-span and reduced incidence of cancer
- Treatment with melatonin or platoquinones increased the life span and reduced the incidence of cancer of aging mice.
- Metformin increased the life span and delayed the development of cancer in mice
Medications that may prevent cancer and aging

- Melatonin
- Plastoquinones derivatives
- SRT-501 (Resveratrol)
- Metformin
La rapamicina aumenta il “Life-span” dei topi

Harrison et al, Nature,, 2009, 460, 392
Augmente de l’espace vital du souris

Skulacev VP: Biochemistry (Mosc) 2007
Aging and tumor growth

Seed

Ground

Gardener
# Tumor biology and aging

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Prognosis and age</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute leukemia</td>
<td>worse</td>
<td>Seed \ Stem cell leukemia</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>worse</td>
<td>Ground \ Il6</td>
</tr>
<tr>
<td>Breast</td>
<td>Better?</td>
<td>Seed \ Gardener</td>
</tr>
<tr>
<td>Ovary</td>
<td>Worse</td>
<td>Unknown</td>
</tr>
<tr>
<td>Brain</td>
<td>Worse</td>
<td>Seed \ Ground</td>
</tr>
</tbody>
</table>
Distribution of disease risk by age at diagnosis.

Bechis S K et al. JCO 2011;29:235-241
Figure.

Association Between Age at Diagnosis and Disease-Specific Mortality Among Postmenopausal Women With Hormone Receptor-Positive Breast Cancer.
van de Water, Willemien; Markopoulos, Christos; MD, PhD; van de Velde, Cornelis; MD, PhD; Seynaeve, Caroline; MD, PhD; Hasenburg, Annette; MD, PhD; Rea, Daniel; Putter, Hein; Nortier, Johan; MD, PhD; de Craen, Anton; MD, PhD; Hille, Elysee; Bastiaannet, Esther; Hadji, Peyman; MD, PhD; Westendorp, Rudi; MD, PhD; Liefers, Gerrit-Jan; MD, PhD; Jones, Stephen

DOI: 10.1001/jama.2012.84

Figure. Cumulative Incidence of Death Due to Breast Cancer, Other Causes, and All Causes by Age at Diagnosis.
Other-cause death is defined as all causes except breast cancer (second primary tumor, endometrial cancer, cardiac disorder, thromboembolism, pulmonary disorder, cerebral disorder, vascular disorder, other causes, and unknown causes).
Conclusions

Aging and cancer are controlled by:

- Oxidative damage
- Caretaker et gatekeeper genes
- Balance of FOXO et SIRT deacetylases
- The system insulin, IGF-IGFR
- Proliferative senescence of fibrobalsts and lymphocytes
- Inflammation
Conclusions

- Cellular senescence is a protective mechanism against cancer.
- Proliferative senescence of fibroblasts and lymphocytes may cause cancer.
- Loss of apoptosis by aging cells may lead to cancer.
Conclusions

- The reduction of the oxidative damage may reduce the risk of cancer and increase life span
- P53 amplification may reduce the risk of cancer without increasing the life span
- The suppression of insulin production may prolong the life span and delay the incidence of cancer
The wrong way to look at cancer and aging