Progress in understanding the biology of aging

by
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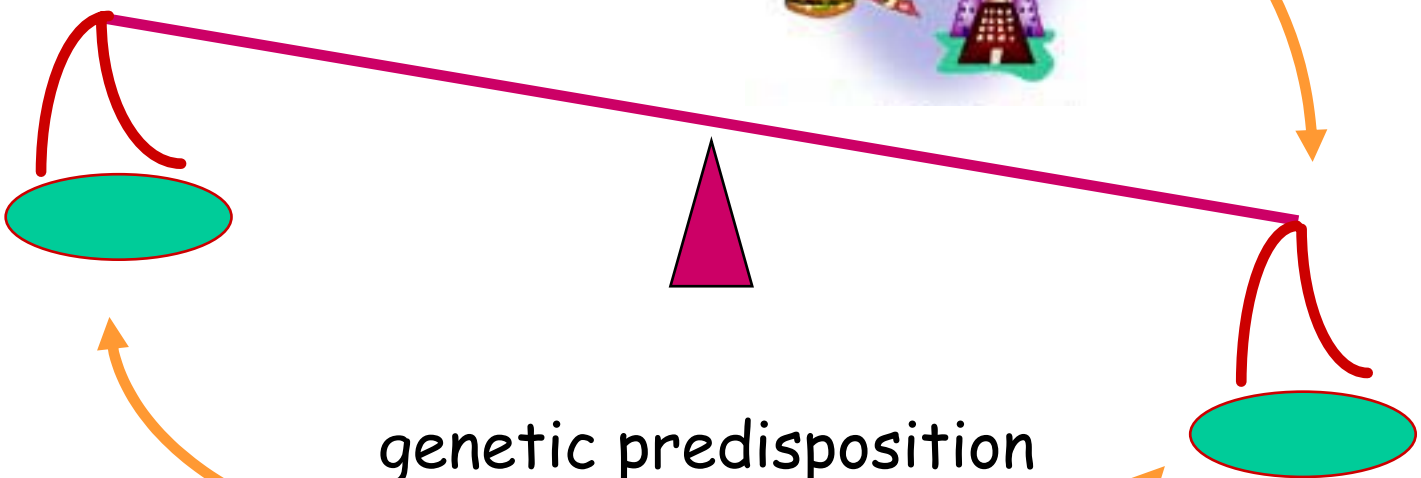
Genetic and Environmental Factors influencing Aging

and cancer

biological age
environment
endogenous damage
ROS

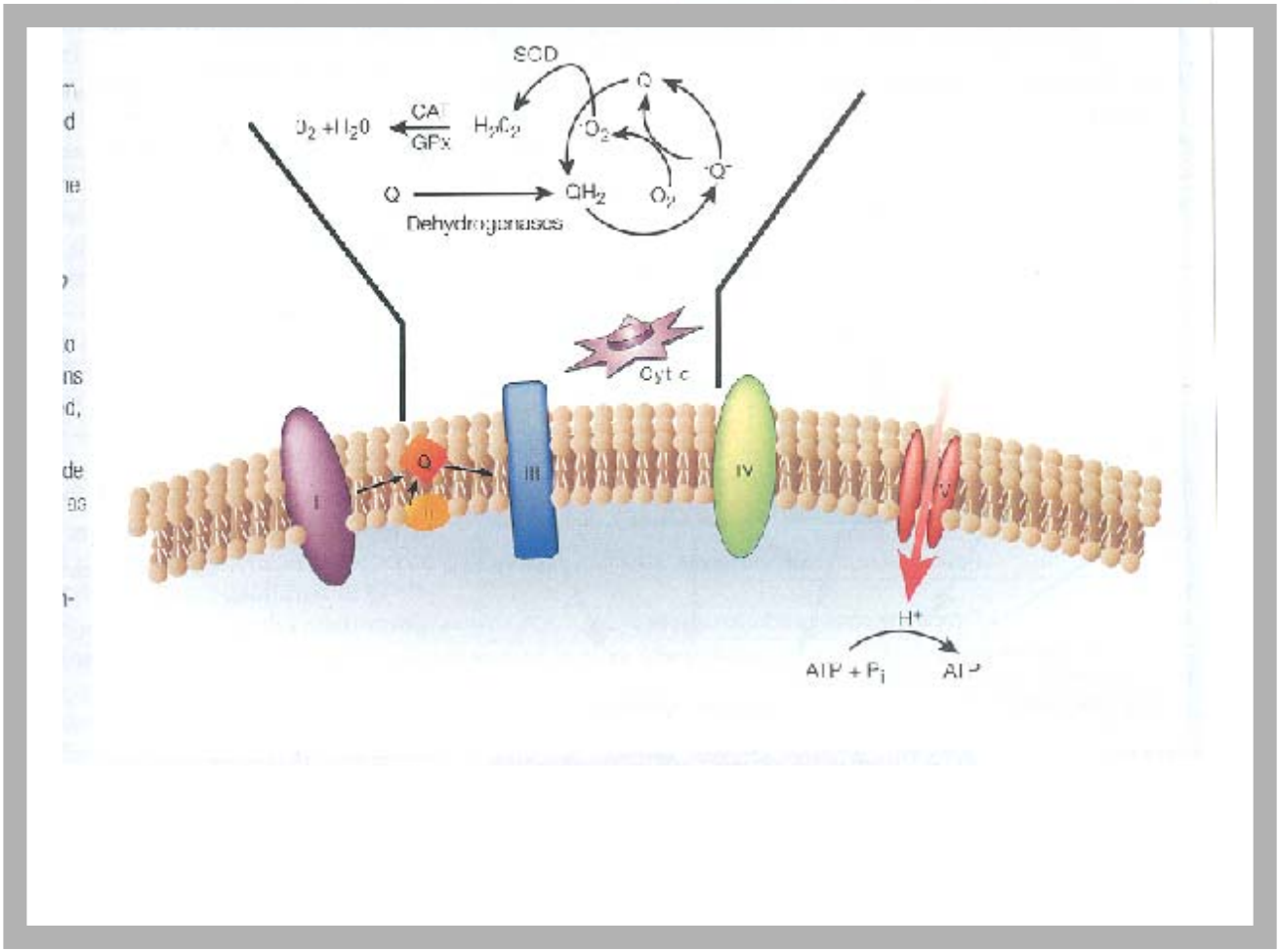


genetic predisposition
(longevity genes,
repair genes,
Anti-oxidants)

The Mechanisms of Aging

- Oxidative stress
- Mitochondrial mutations
- Repair
- Caloric restriction-insulin signaling
- Replicative senescence
- Epigenetic changes

Endogenous production and accumulation of ROS



The effect of ROS on aging

- On the cellular level
  - DNA mutations
  - Protein modifications
  - Lipid modifications
- On the tissue level
  - Cellular senescence (cardiac insuffic.)
  - Chronic diseases (fibrosis)
  - Malignant transformation (cancer)

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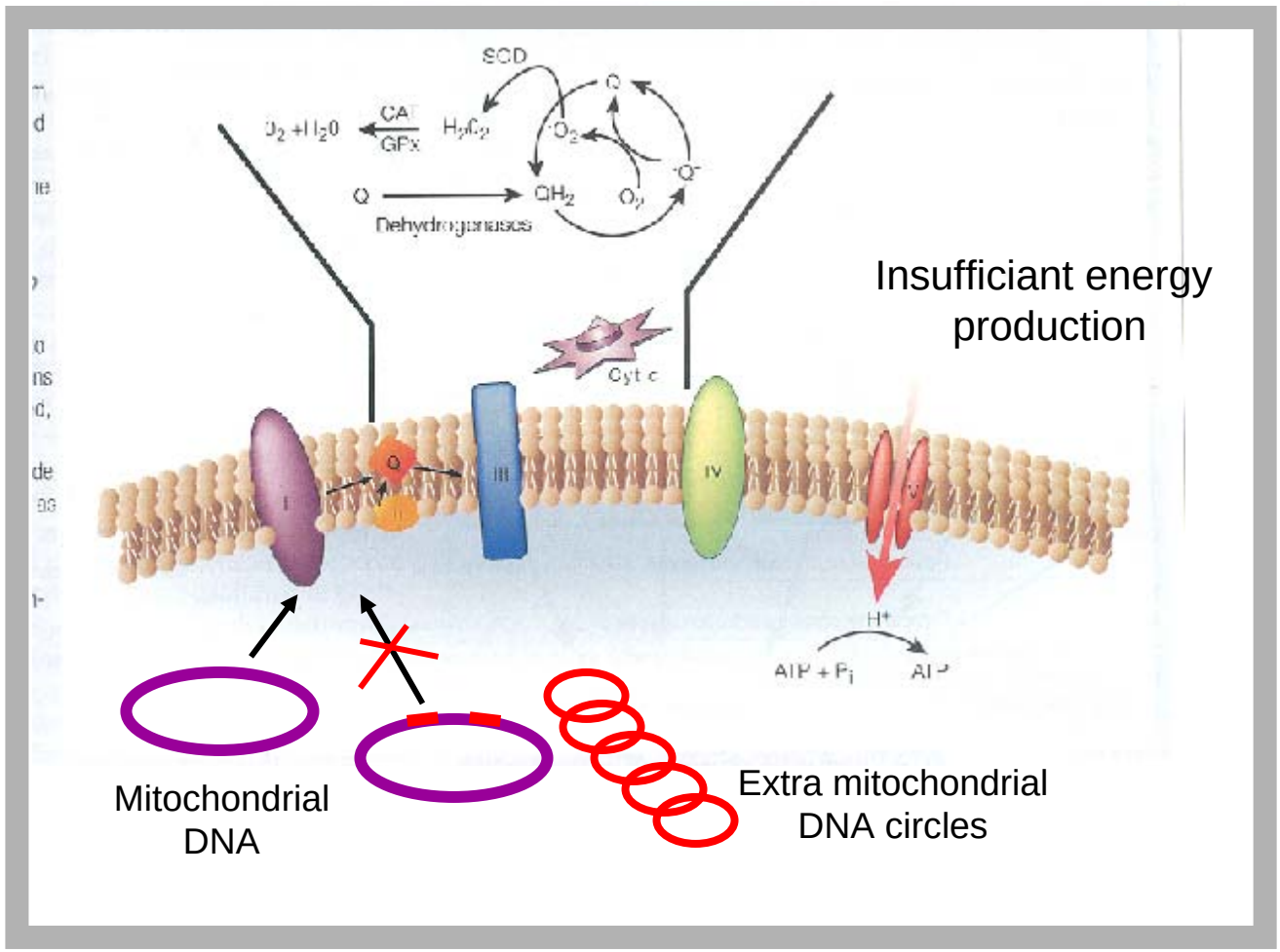
Mitochondrial mutations



The effect of mitochondrial mutations on aging

- On the cellular level
  - Less efficiant respiration
  - Increased production of ROS
  - Increased accumulation of damage
- On the tissue level
  - Cellular senescence (cardiac insuffic.)
  - Chronic diseases (fibrosis)
  - Malignant transformation (cancer)

- Amplification of endogenous damage by ROS

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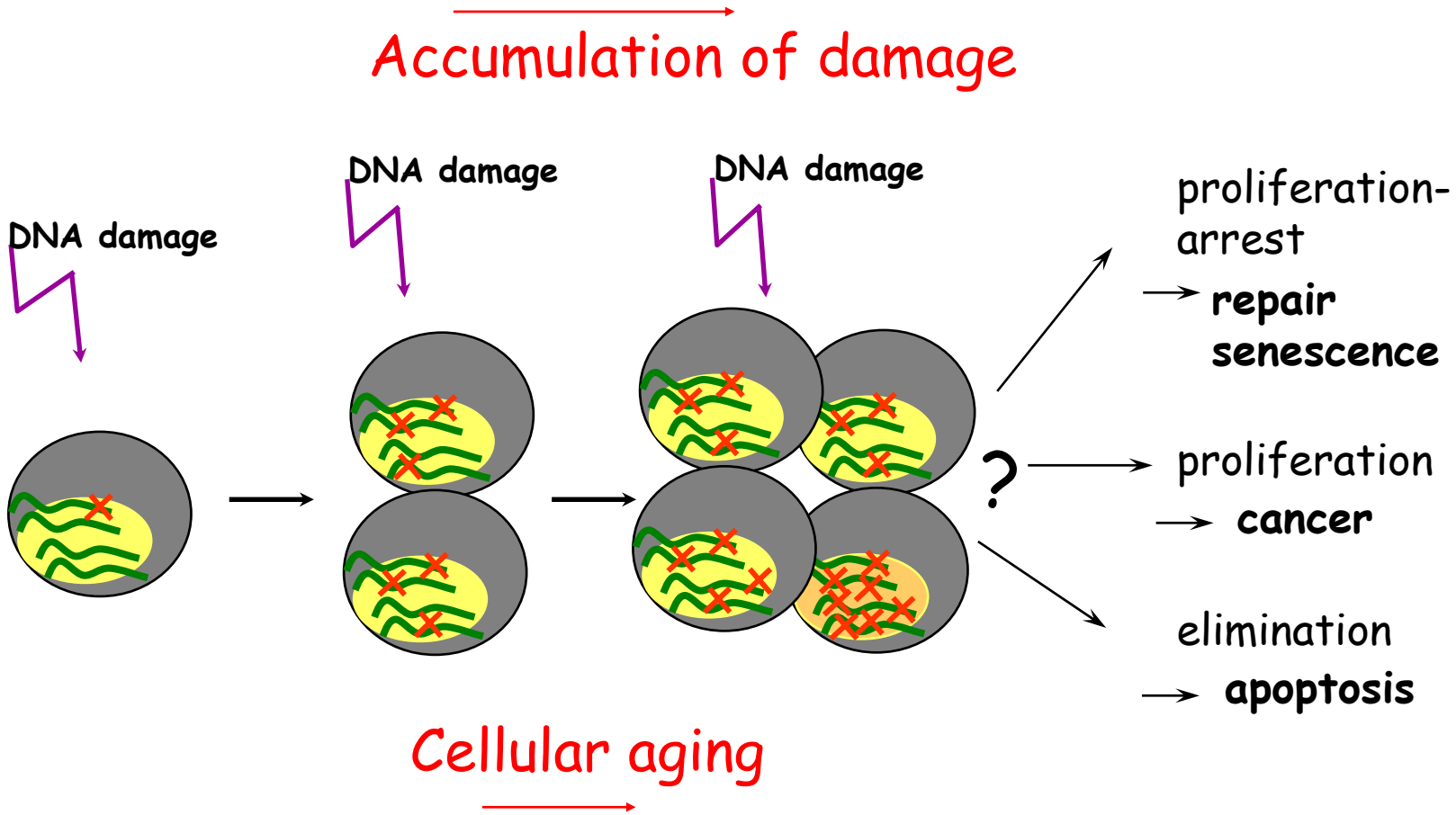
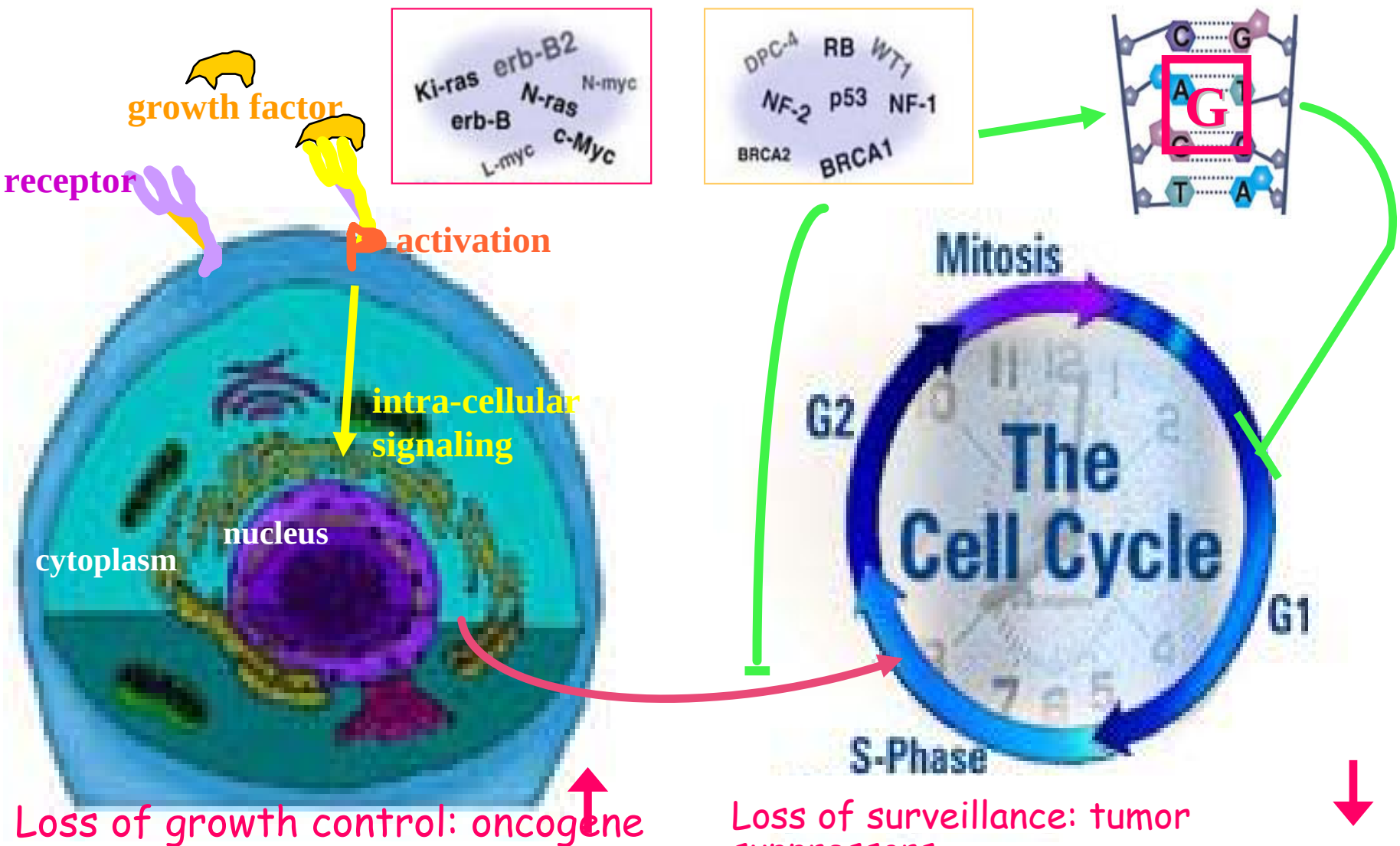
Age-dependent decline of repair



Repair, senescence, or die



The Mechanisms of Aging

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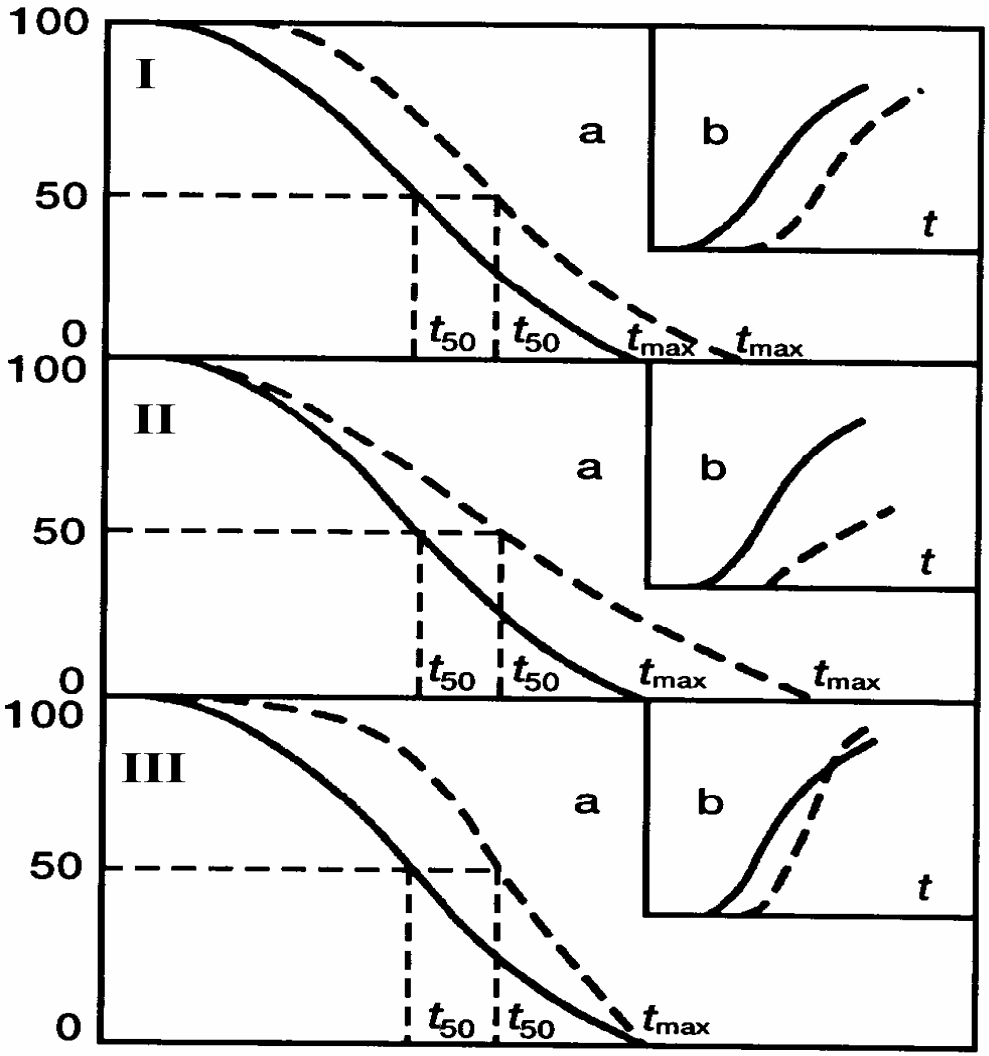
Can calorie restriction (CR) influence aging ?

- On the cellular level
  - Less ROS production
  - Less damage
- On the tissue level
  - Less senescence (cardiac insuffic.)
  - Less apoptosis (fibrosis)
  - Less malignant transformation (cancer)

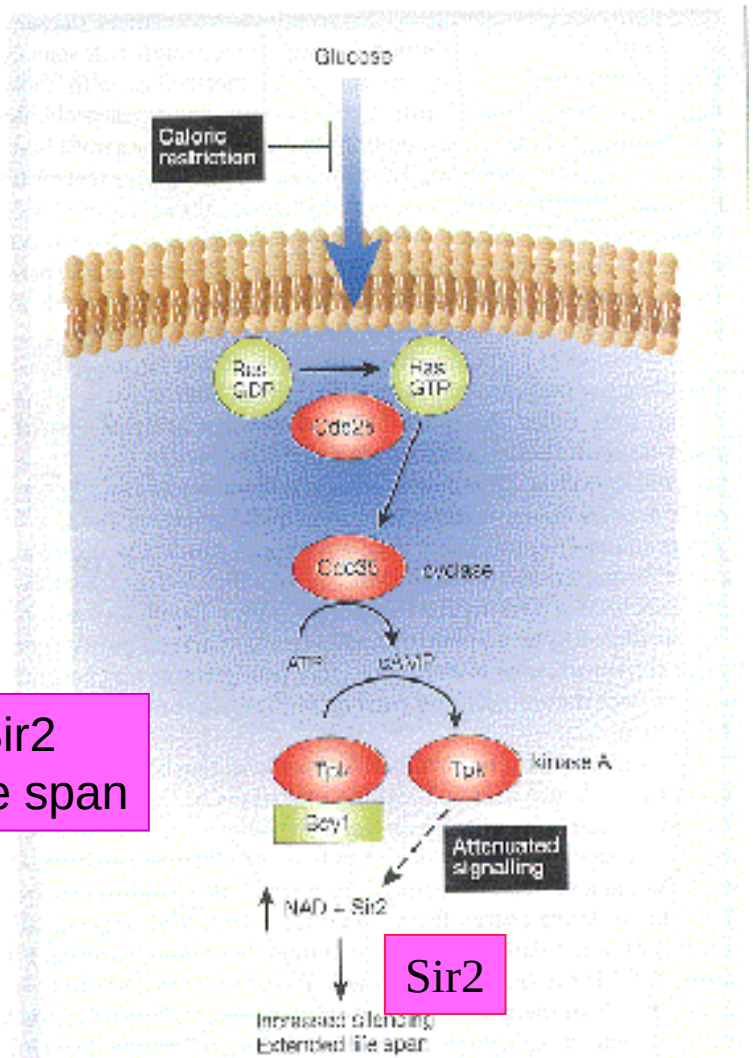
- Reduction of endogenous damage by ROS

Increase in lifespan by CR



Guarante, 2000; Anisimov, 2001

Is CR acting on more than ROS production?



Caloric restriction

Intracellular signaling

Reduced silencing
(altered gene expression)

Yeast mutants of Sir2
Have shortened life span

Sir2 is increasing silencing

The mechanisms behind the CR benefit for life-span

- CR induces physiological changes
  - Lowered serum glucose
  - Lowered cholesterol levels
  - Increase in insulin sensitivity
  - Decrease in oxygen consumption and body temperature
- CR molecular pathway
  - Activation of Sir2 by binding to NAD
  - NAD links activity of Sir2 to energy status
  - Sir2 is a Histone-deacetylase=**silencer**
- CR reduces ROS and induces silencing

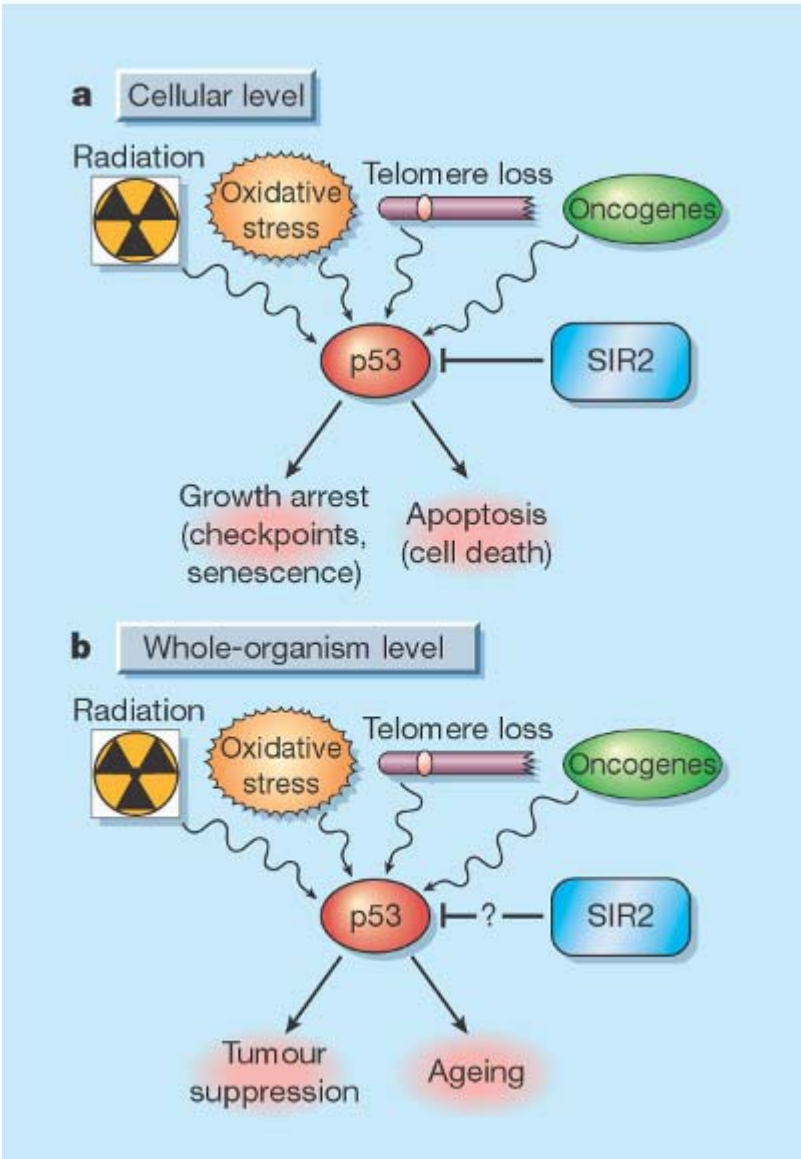
A link between caloric restriction and cancer?

- Caloric restriction can postpone the aging process
- Reduced metabolism and decreased production of associated endogenous damaging agents
- Reduced glucose signaling, increased silencing

Tumor suppressor p53 joins aging

- P53 most frequently mutated in cancer
  - mP53 hyper-stable mutant> high p53 activity
  - mP53 mice are resistant to tumors
  - mP53 mice live less long and age prematurely
- P53 molecular link to aging
  - P53 associates with Sir2
  - Association with Sir2 inhibits its activity
- Too much of a good thing is bad…

Molecular link of p53 to aging



Tyler, 2002; Kirkwood, 2002

The Mechanisms of Aging

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The theory of replicative senescence

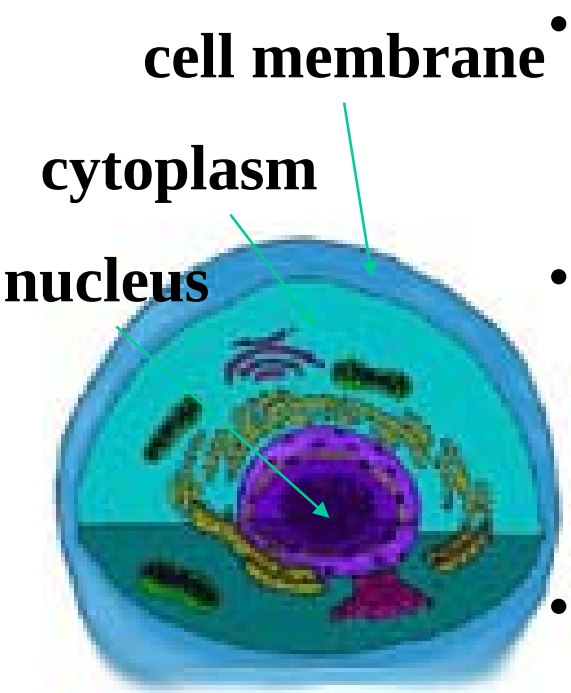
- Normal somatic cells have a finite potential to divide when cultured in vitro: ~ 50 cell divisions
- When the number of possible cell divisions is reached cells irrevercibly enter a quiescent state (Go)
- Immortal cells are abnormal and most have properties of cancer cells

Hayflick theorie.

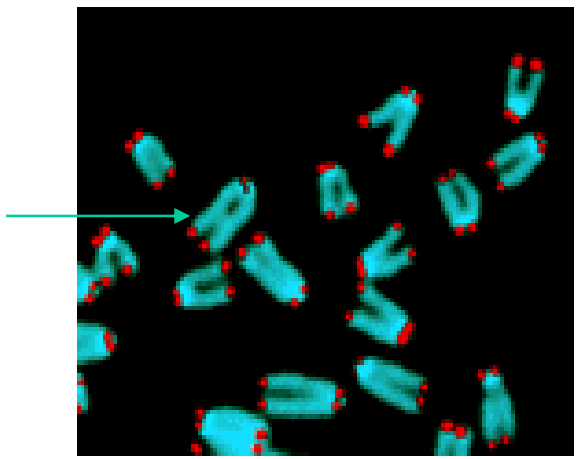
- 40 years ago *Hayflick and Moorehead* suggested that a counting mechanism existed in normal cells *(Hayflick limit)*

- This *replicometer* has been identified as the telomere shortening mechanism

Telomeres

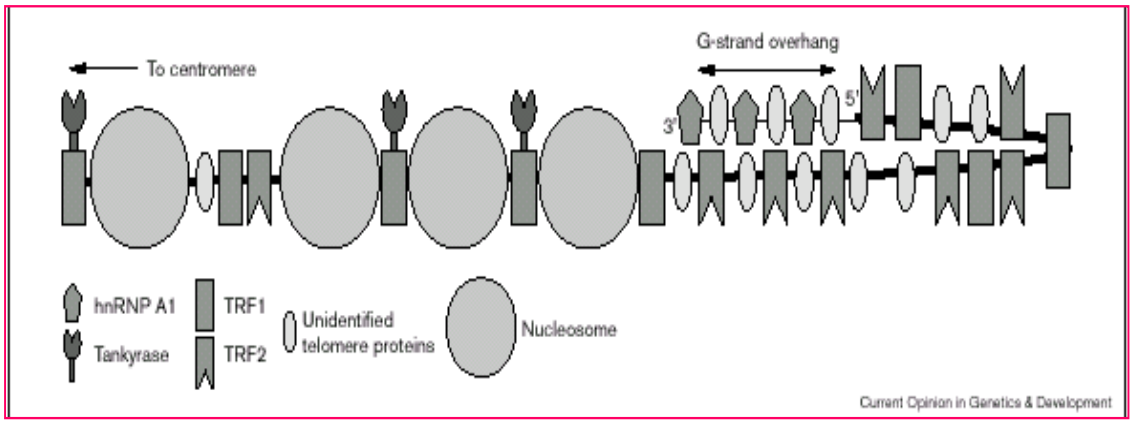


- **Nucleus contains chromosomes (DNA and protein)**
- **Telomeres are special structures at the end of chromosomes**
- **Telomere DNA consists of non-coding repetitive sequences**



Blasco et al., 1997

Telomere structure and function

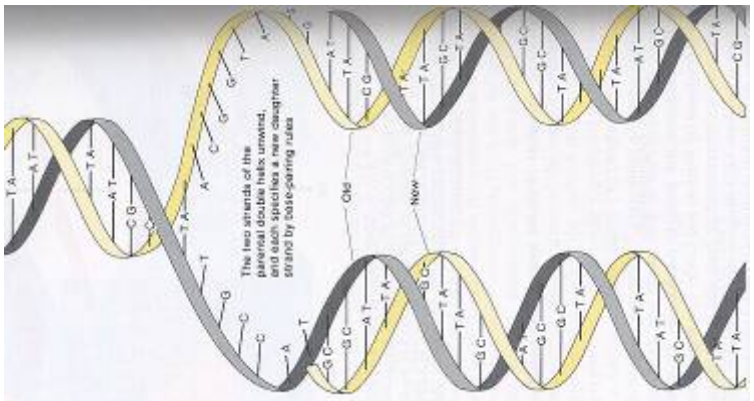


Telomere: a nucleoprotein complex

- **protects chromosomes against degradation, rearrangements, and fusion with other chromosome ends**
- **protects against erosion of coding regions (~ 200 bp per cell division)**
- **telomere shortening is consistent with a telomere-based counting mechanism.**

The mechanism of telomere shortening

DNA replication mechanism

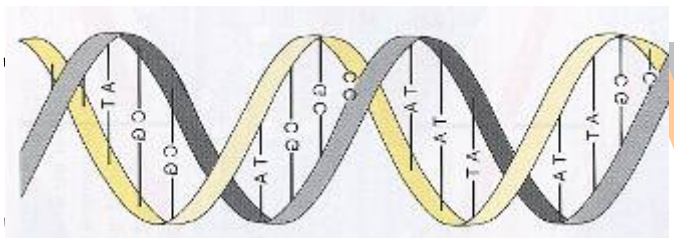


3’

5’

New synthesis RNA primer

The end replication problem



TTGGGGTTGGGGTTGGGGTT

G 3’

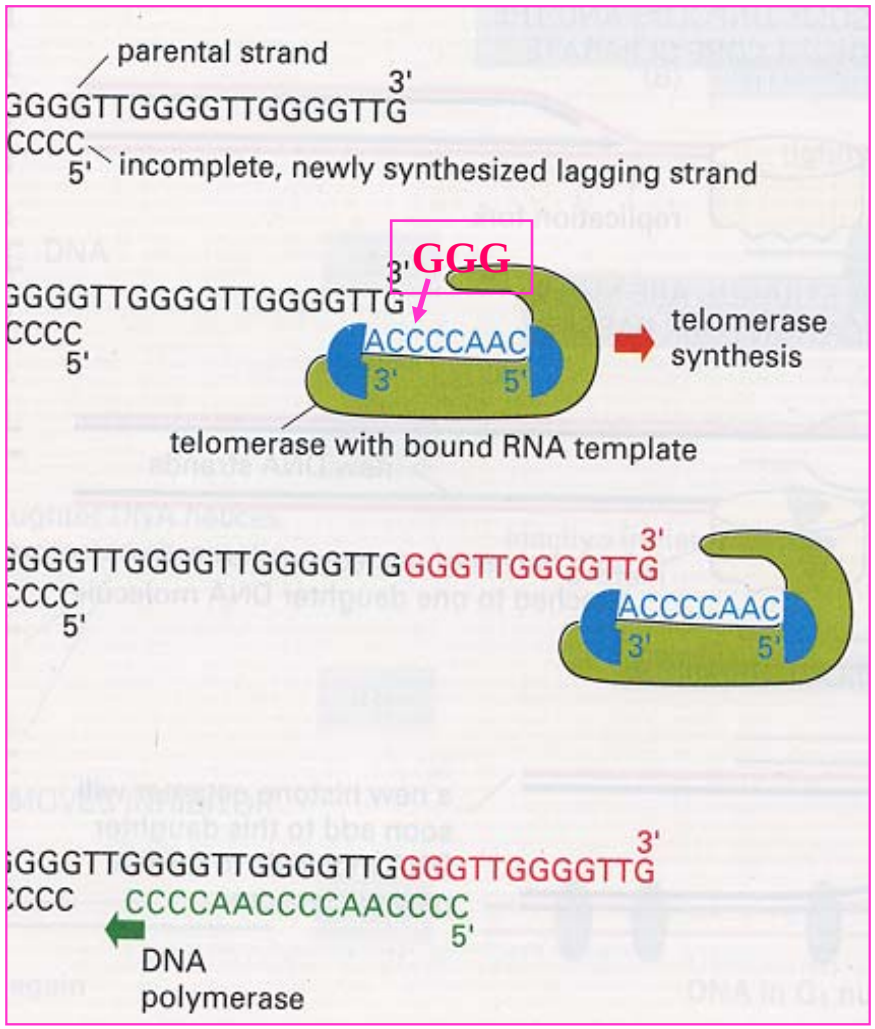
AACCCC 5’

Incomplete newly synthesized strand

Coding sequences - genes Telomer-repeats 5-20 kb

Telomerase or the illusion of immortality

- **The enzyme telomerase adds nucleotides to the 3'end**
- **Telomerase can compensate telomere shortening**



Human diseases linked to telomere erosion

- Patients with Werner's Syndrome (WS) Patients are not only facing premature aging, but telomere shortening, chromosomal rearrangements, and cancer.
- The Bloom's syndrome (BS), characterized by a genetic predisposition to cancer, presents a cellular phenotype similar to WS.
- The Ataxia Telangiectasia syndrome (ATM) is characteristic for shortened telomeres and a predisposition to cancers.

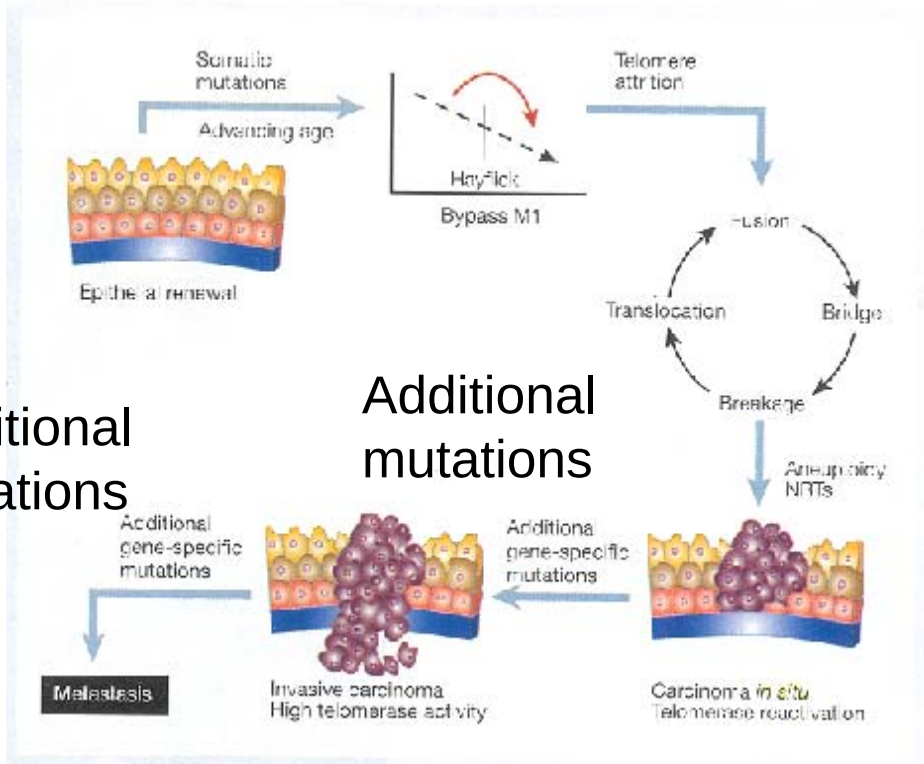
Mice deficient for telomerase

- Mice have longer telomeres than humans
- In old mice epithelial cell derived tumors are not typical
- Mice deficient for telomerase, show critical telomere shortening after 6 generations
- Telomerase deficient mice have more tumors and of epithelial origin
  (DePinho, 2000; Chang, 2001)

Importance of telomeres status in cancers

Somatic mutations

Telomere attrition

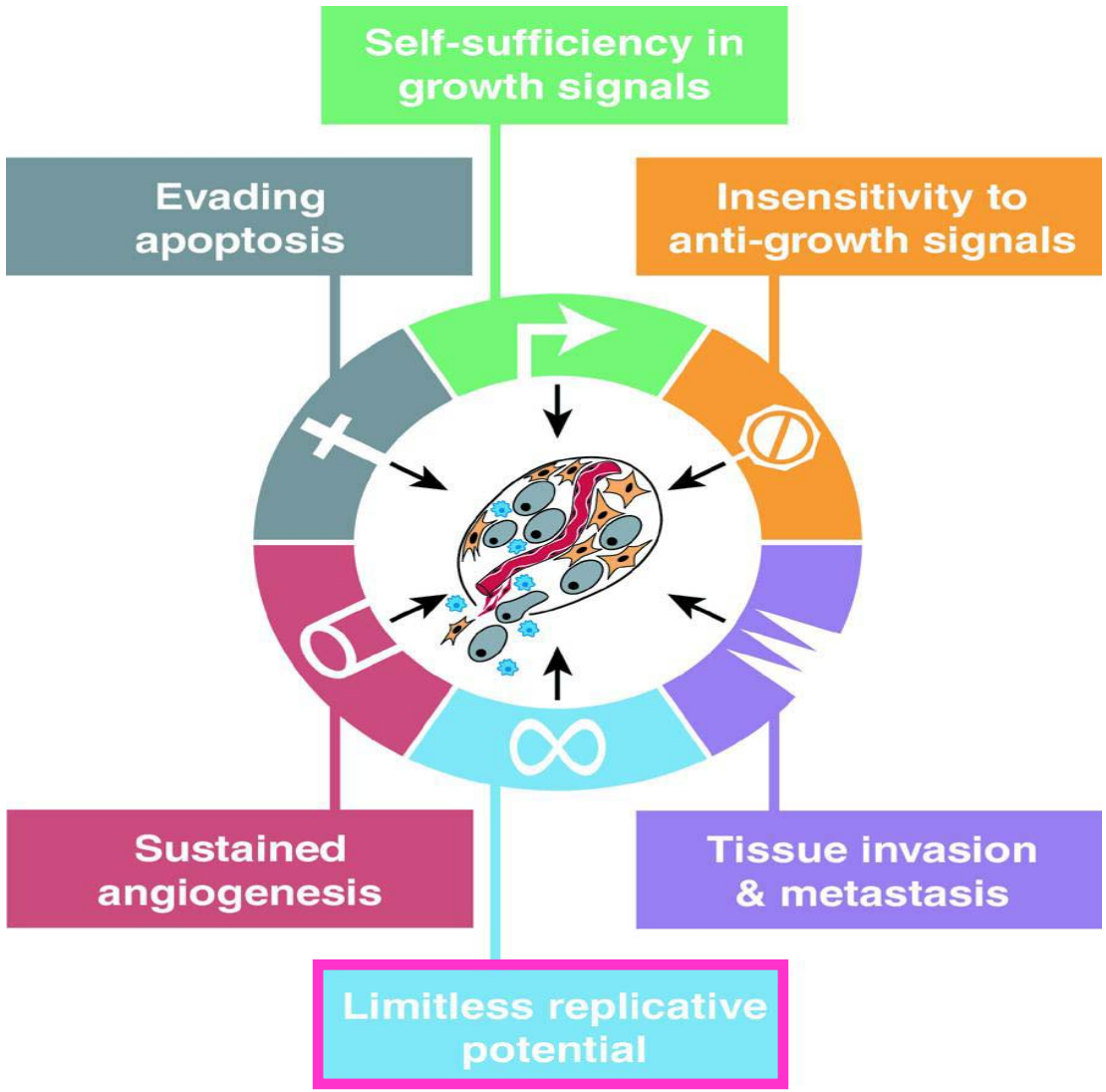


Additional mutations

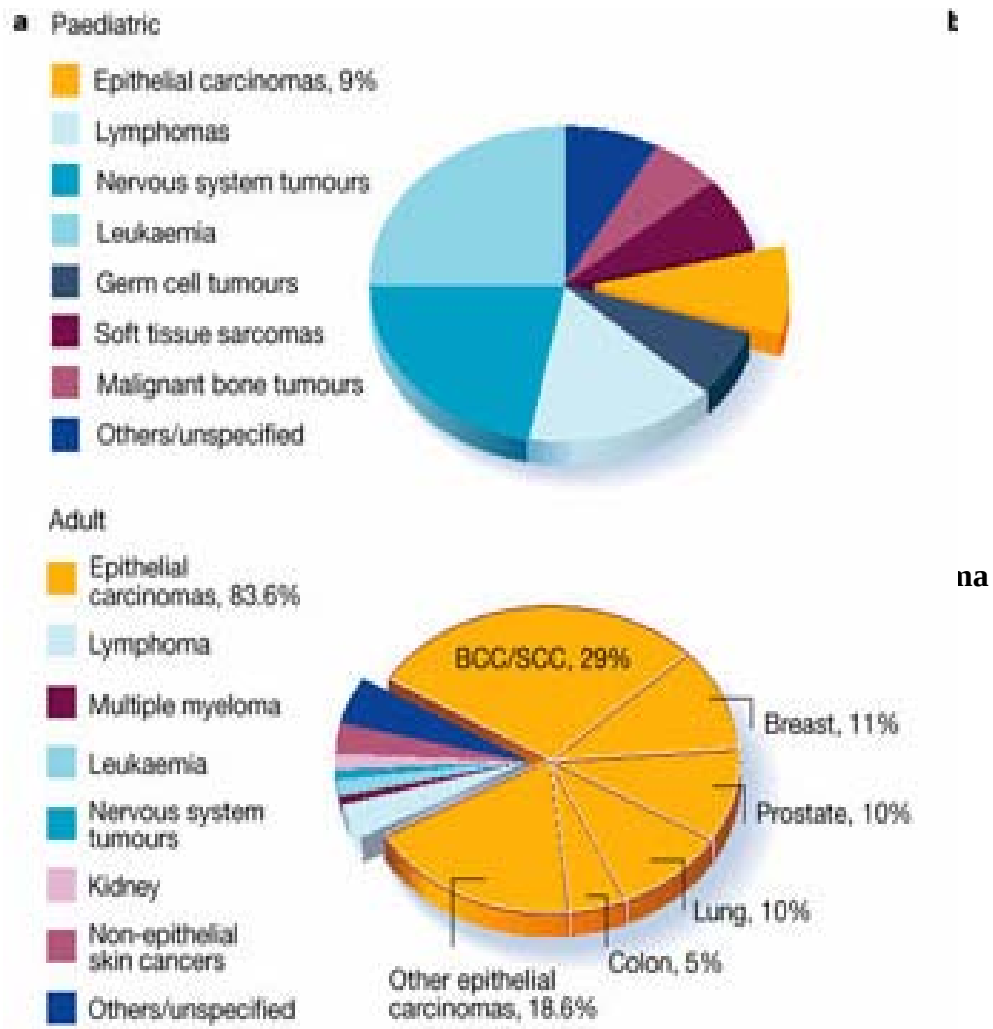
Additional mutations

aneuploidy

Multiple steps towards malignancy

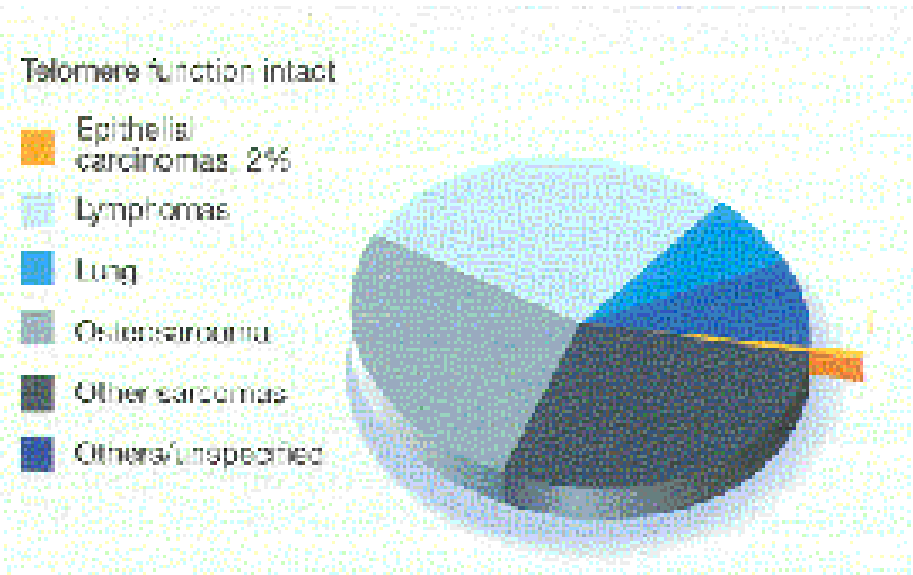


Replicative senescence linked to epithelial cancers?

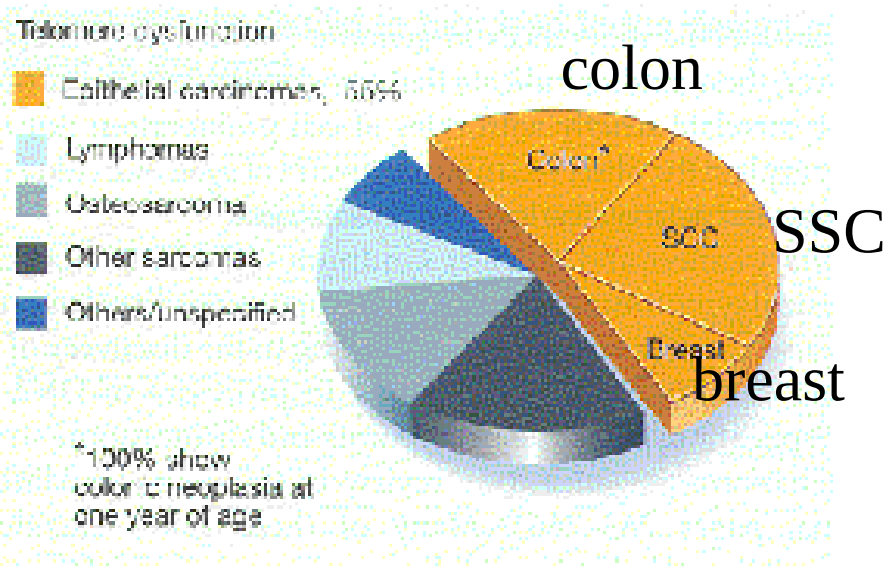


Telomere function in cancers

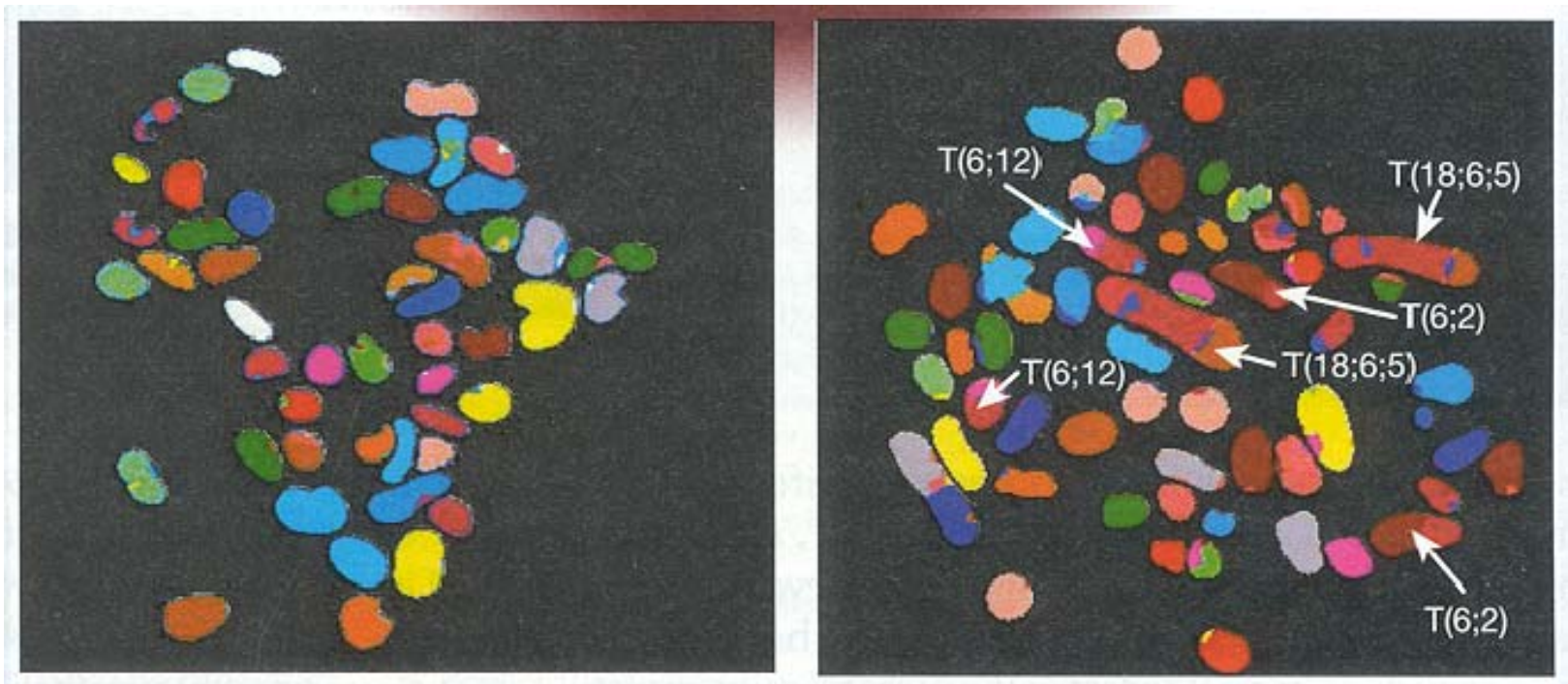
Telomere function intact



Telomere disfunction



Telomeric instability in cancers



Spectral caryotype profile
DePinho, 2001

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Epigenetic changes

- Genetics: inheritance of information based on gene sequence
- Epigenetics: inheritance of information based on gene expression level
  - hypermethylation in GpC islands – effecting gene expression- silencing
  - hypomethylation derepression genome wide
- Epigenetics can be influenced by environmental factors

Methylation

- Methylation is a host defence mechanism for repression of parasitic DNA sequences
- Methylation cascade of events
  - Transcriptional silencing
  - Genome hypomethylation
  - Loss of imprinting
  - Defects in chromatin related genes> transformation

Epigenetic modifications are reversible=therapeutics

Richard Peto:

« There is no such thing as aging and cancer is not related to it »

Breast Cancer: A Model to Study Cancer and Aging

- **Tumor biology altered with aging**
  - **Growth factor receptors like ErbB2/HER2**
  - **Zn-finger receptors & gene regulators like ER**
- **Tumor therapy altered with aging?**
  - **anti-ErbB2/HER2 agent: Herceptin/trastuzumab**
  - **anti-ER agents: tamoxifen, aromatase inhibitors**

Age-related biomarkers?

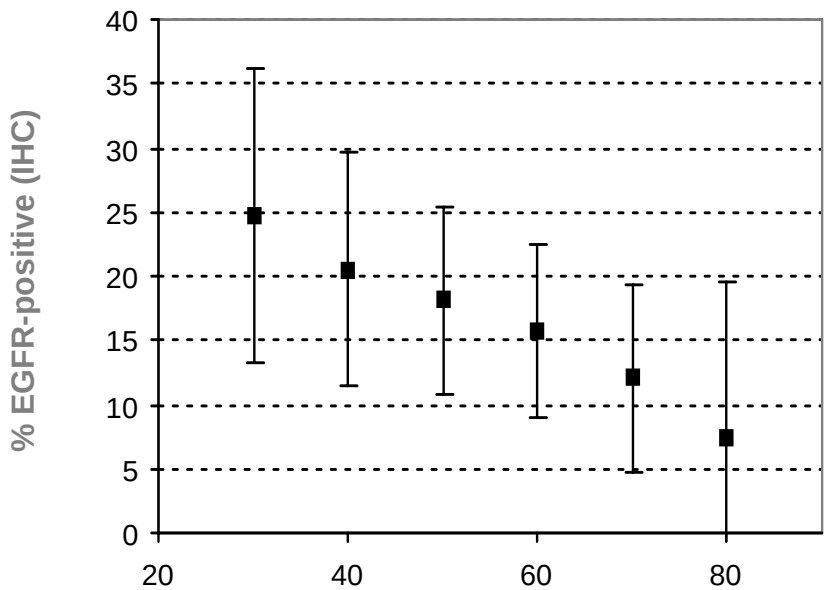
- **Most have no association with age**
  - ***PR, pS2, Bcl-2, EGFR, VEGF, uPA, uPAR, PAI-1, Cath-D***

- **Some are strongly associated with age**
  - **Negative:** ***grade, MI/MIB-1, AI, p53, ErbB1&2***
  - **Positive:** ***ER positivity & content***

cf. Benz et al., Age-associated biomarker profiles of human breast cancer. Int. J. Biochem. Cell Biol., 2002
Quong et al., Age-dependent changes in breast cancer hormone receptors and oxidant stress markers. Breast Cancer Res. Treat., 2002

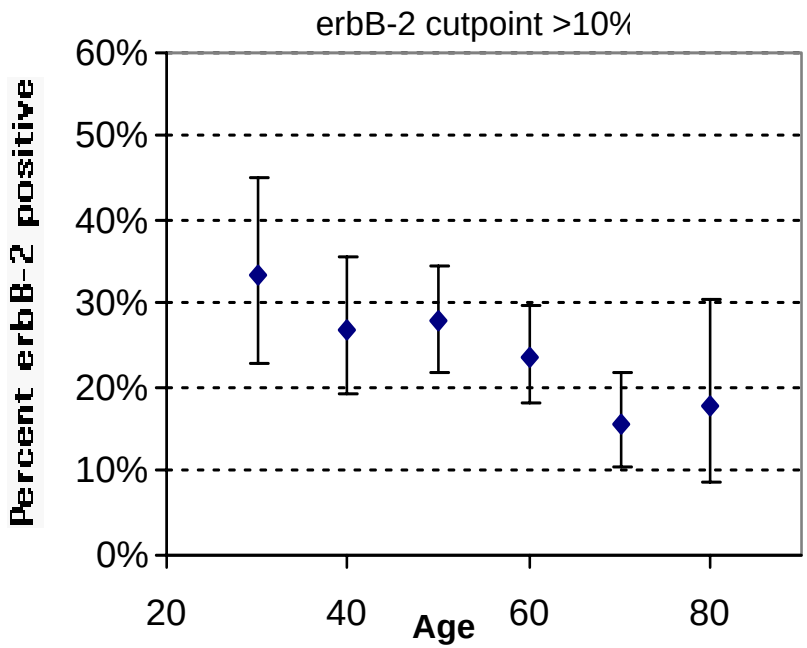
Decline significantly with age after 40 y

EGFR/ErbB1



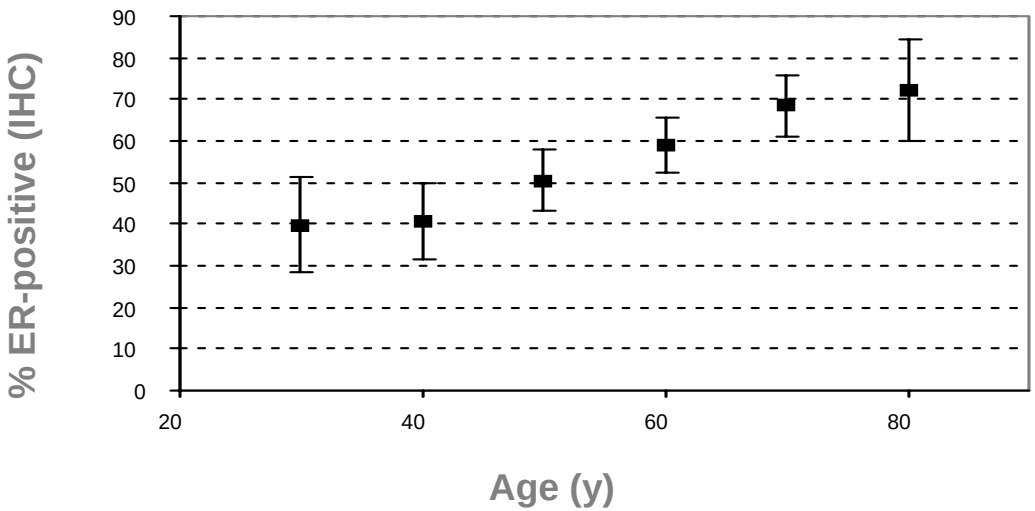
(N = 815; r = -0.170, p < 0.0001)

HER2/ErbB2



(N = 820; r = -0.136, p < 0.0001)

Expression of Estrogen Receptor



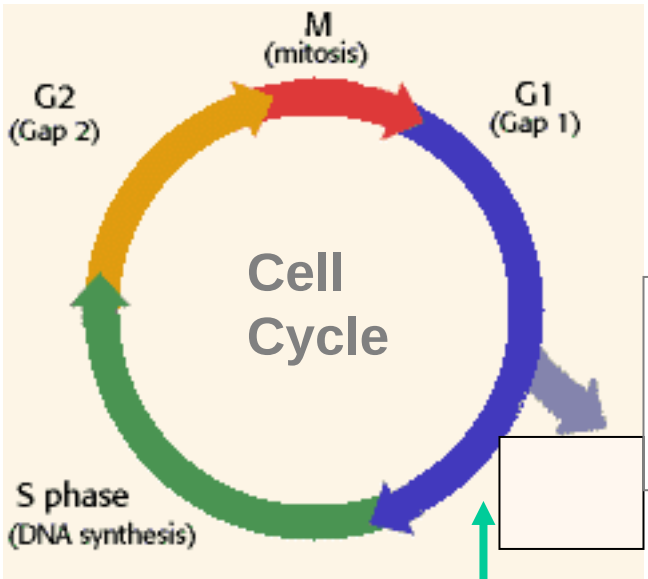
N = 813; r = 0.213, p < 0.0001)

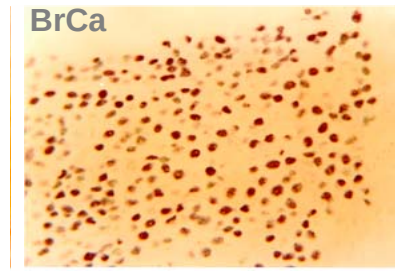
Increase significantly with age after 40 y

Breast Cancer & Aging: Conclusions

- **Aging increases breast cancer incidence and alters breast cancer biology.**

- **ER dysregulation and overexpression accounts for most of the increase in breast cancer incidence after age 50.**





Dysregulated proliferation of ER+ breast epithelium *most characteristic of breast cancers arising after age 40*

ER induced genes:

Cyclin D1

PR, pS2, Bcl2, cath D

ER

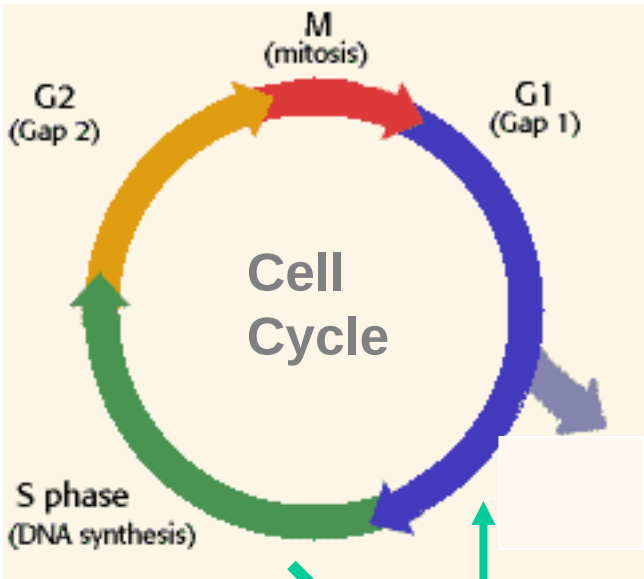
AE

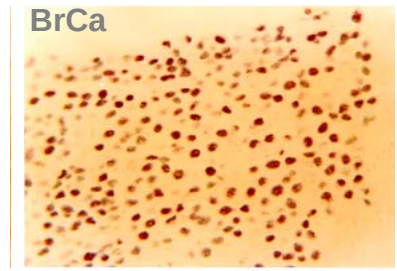
ER

Upregulated ER expression

E_2

ER





Dysregulated proliferation of ER+ breast epithelium *with epigenetically silenced tumor suppressor genes after age 40*

ER induced genes:

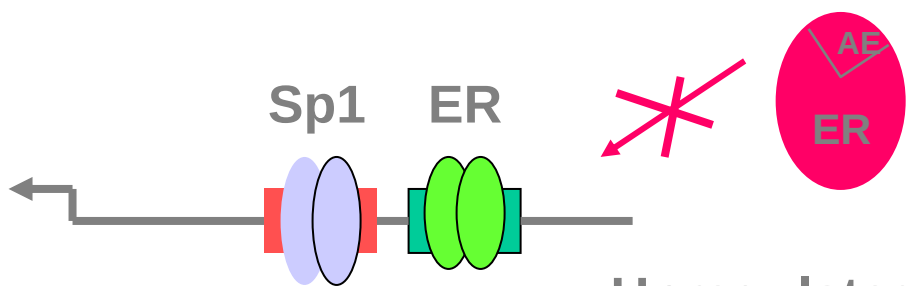
Cyclin D1

PR, pS2, Bcl2, cath D

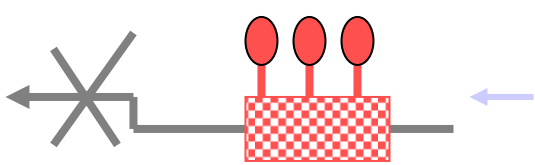
Suppressors:

p14, p16, p21,

RB, BRCA1



Upregulated ER expression



Methylated Sp1 GC box
silenced by DNMT proteins

Cancer risk correlated with age

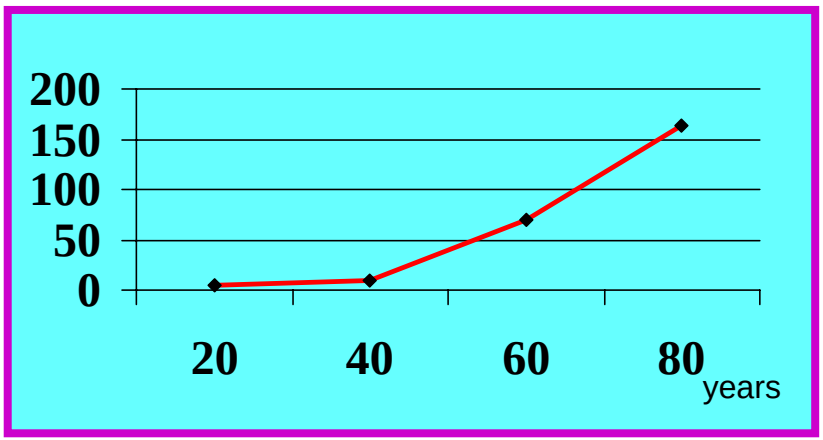
Increase of life expectancy=increased exposure to carcinogens and aging

Mechanisms of Aging and Cancer

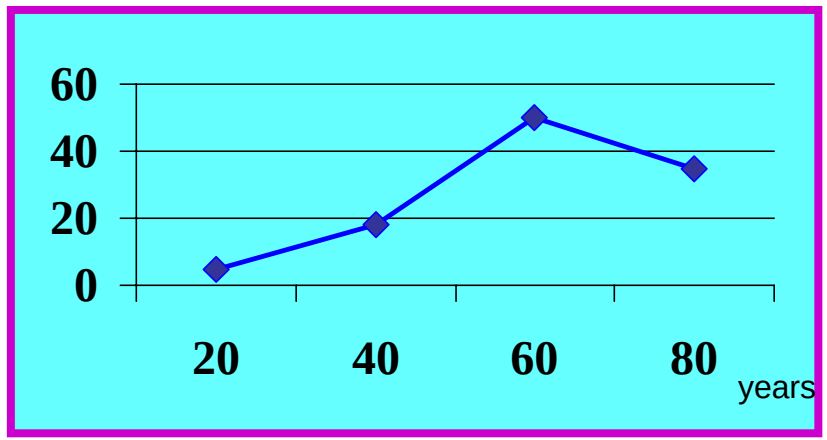
- Is the rate of aging similar in different tissues?
- OR
- Is the susceptibility to carcinogenesis the same in different tissues at different age?
- Anisimov, 2001

Age-related distribution of cancer in different tissues

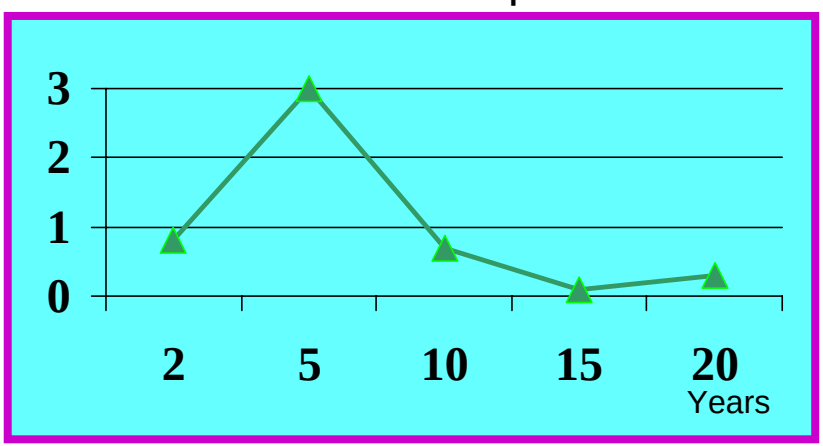
Stomach cancer



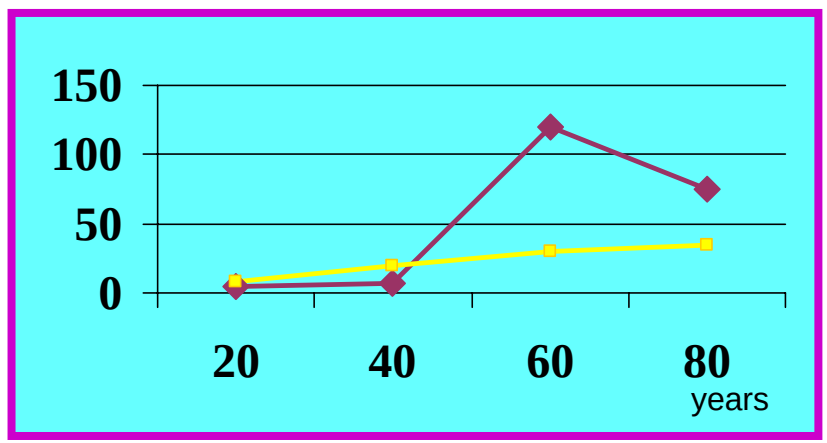
Breast cancer



Nephroblastoma



Endometrial and cervical cancer



AGING AND CARCINOGENESIS

INITIATION

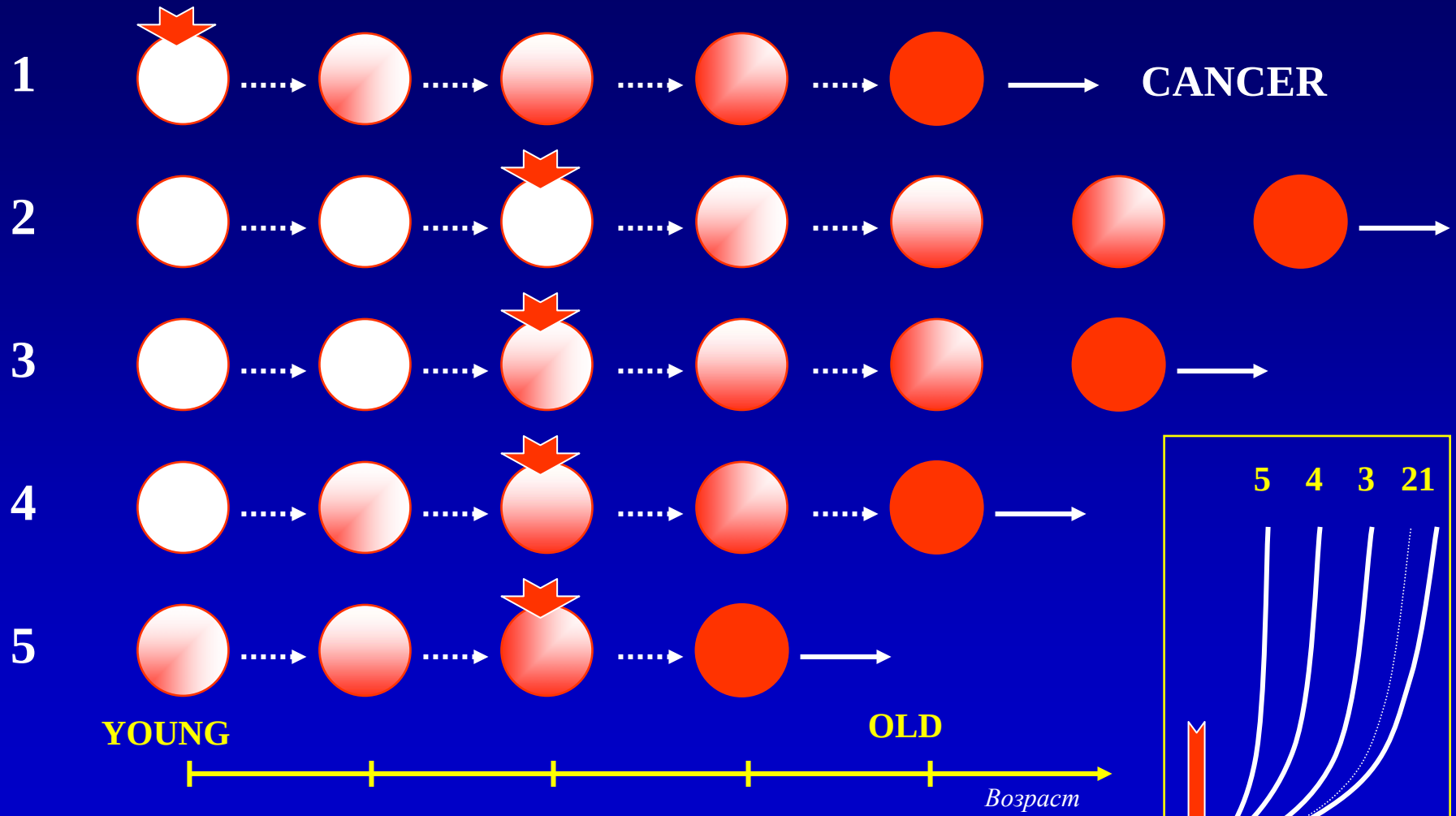
- genetic predisposition
- pharmacokynetics and pharmacodynamics
- DNA repair
- proliferative activity
- apoptosis

PROMOTION

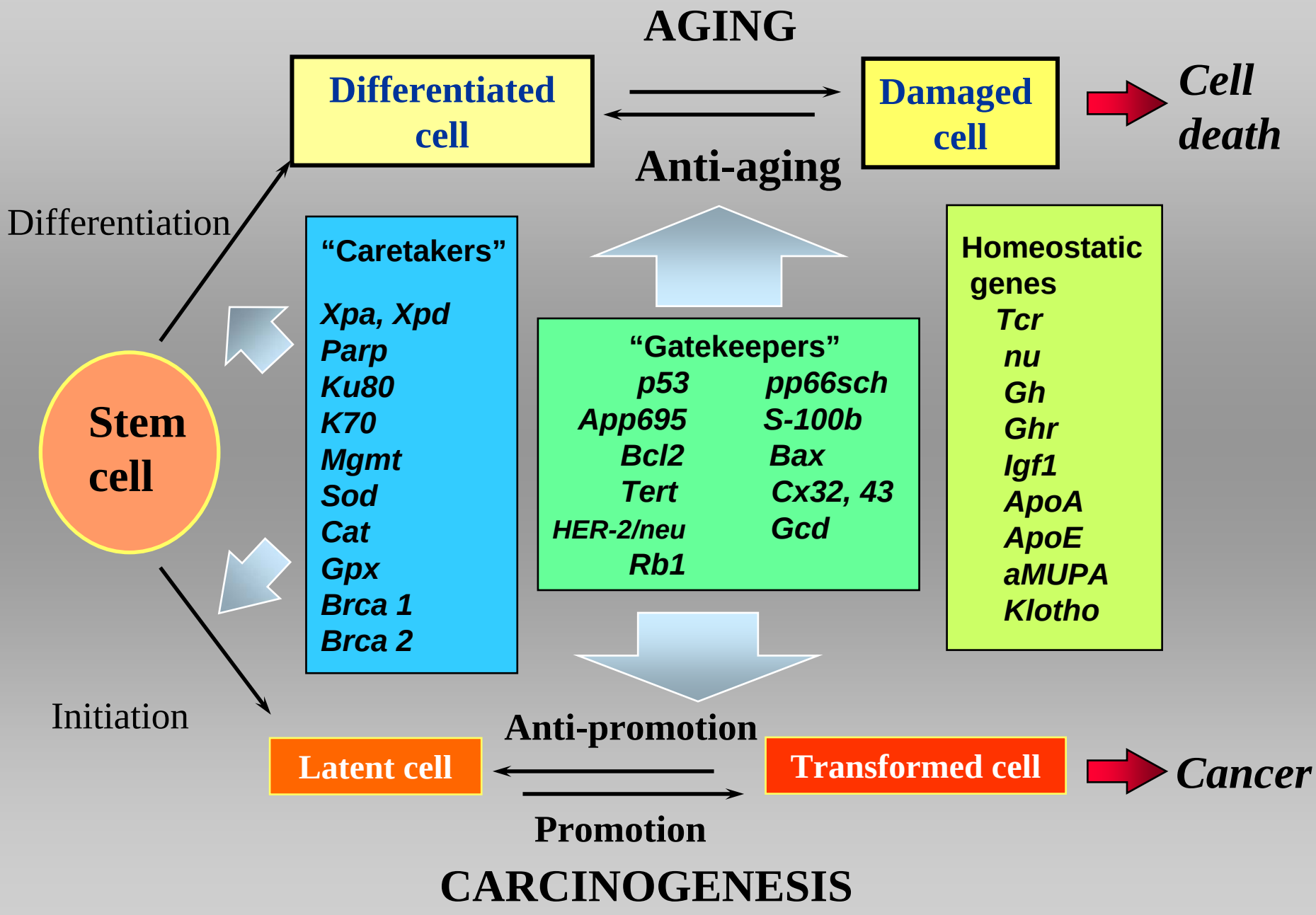
- immunesenescence
- changes of lipid and carbohydrate metabolism
- insulin, IGF-1,
- triglycerides, LDL
- hormones (GH, FSH, LH, prolactin, sex steroids)
- growth factors

Aging is accompanied by accumulation of premalignant lesions in target tissues

MULTI-STAGE CARCINOGENESIS and AGING



Anisimov V.N., 199


AGING
Differentiated cell
Damaged cell
Cell death
Anti-aging
Differentiation
"Caretakers"
Xpa, Xpd
Parp
Ku80
K70
Mgmt
Sod
Cat
Gpx
Brca 1
Brca 2
"Gatekeepers"
p53
pp66sch
App695
S-100b
Bcl2
Bax
Tert
Cx32, 43
HER-2/neu
Gcd
Rb1
Homeostatic genes
Tcr
nu
Gh
Ghr
Igf1
ApoA
ApoE
aMUPA
Klotho
Stem cell
Initiation
Anti-promotion
Latent cell
Transformed cell
Cancer
Promotion
CARCINOGENESIS

Life itself is lethal, and what makes it sweet makes it more lethal