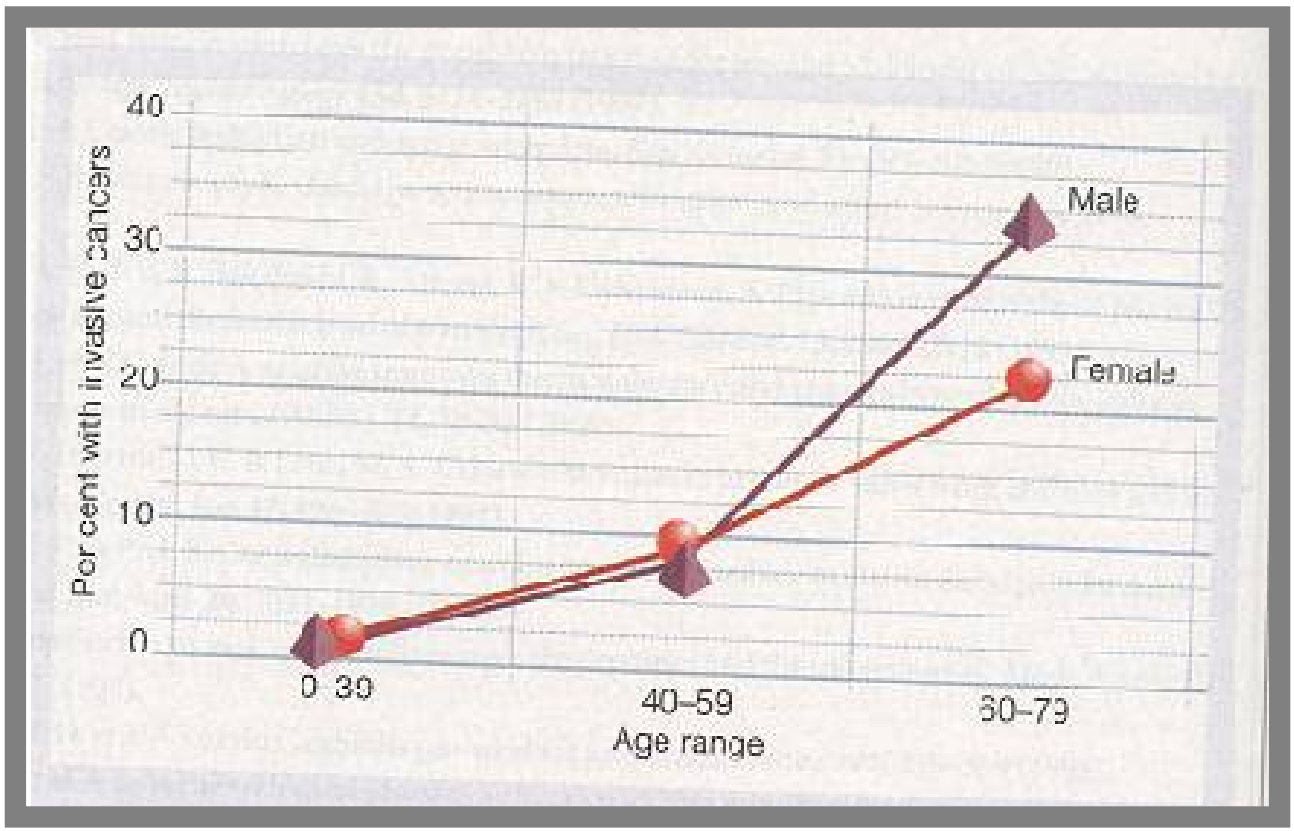
Aging research on cancer

Irmgard Irminger-Finger
Louis Jeantet Laboratory of Aging Biology

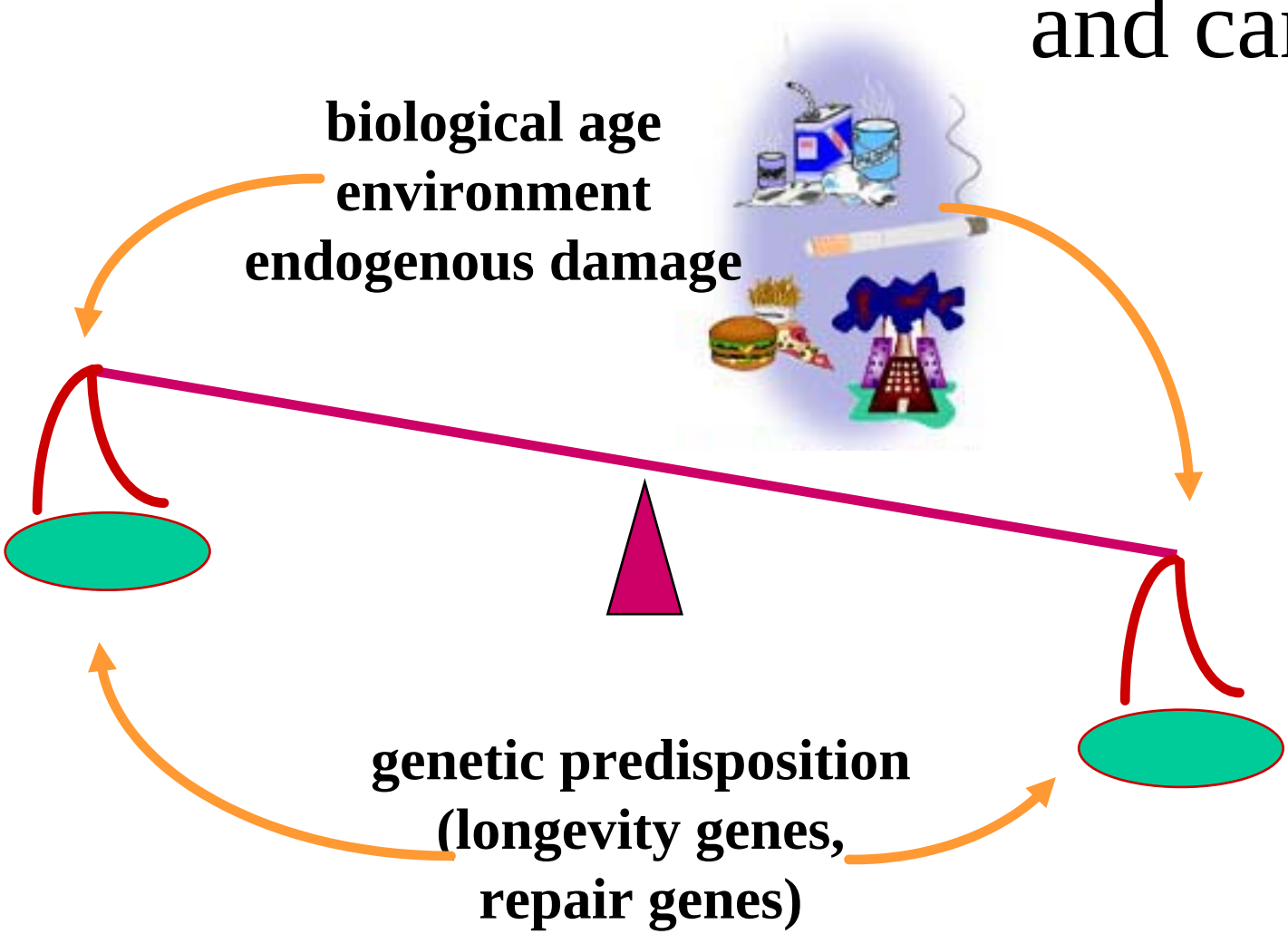
Department of Geriatrics
University of Geneva

Possible mechanisms linking increasing cancer risk to aging

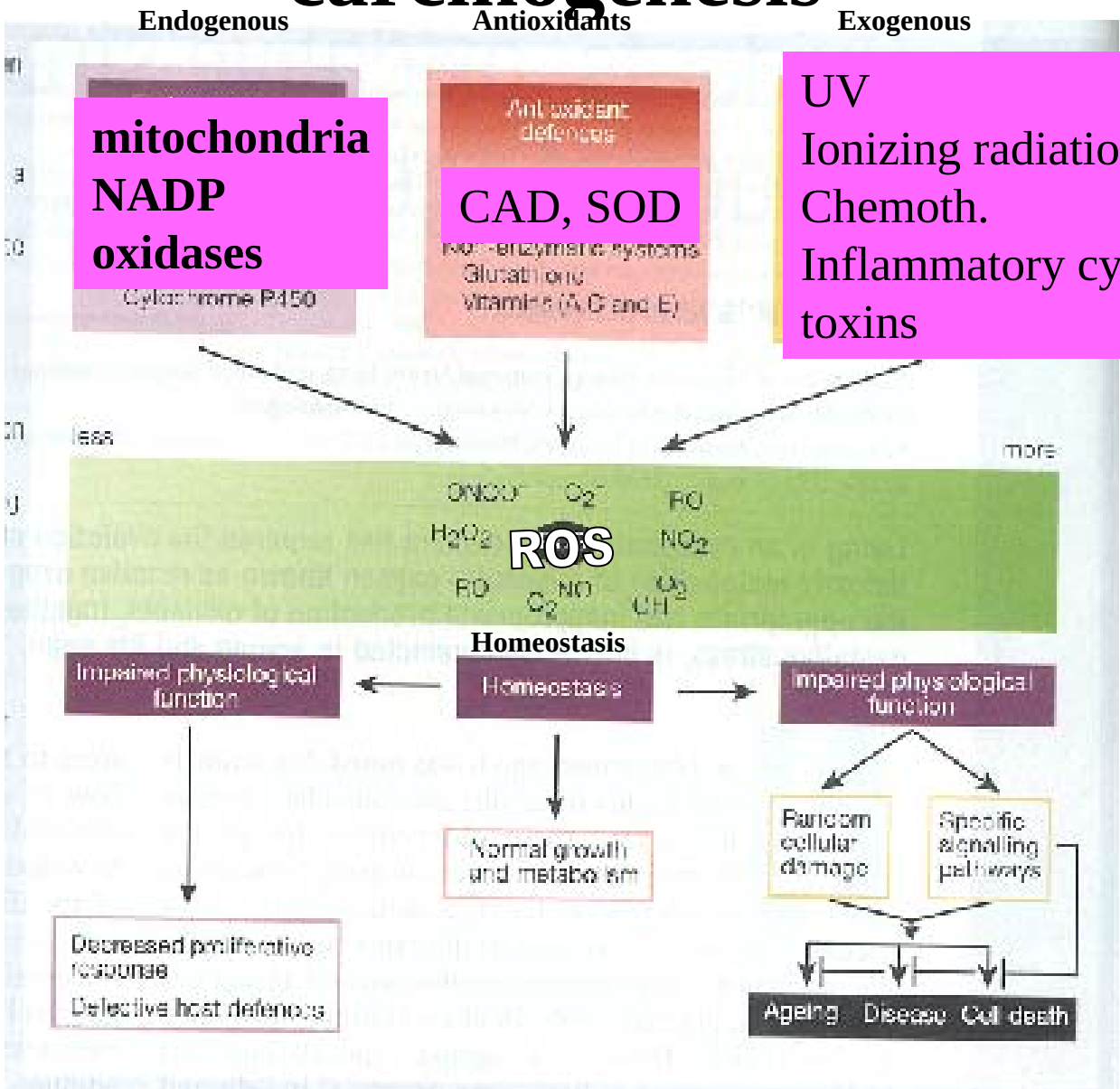
Age is the biggest risk factor for cancer



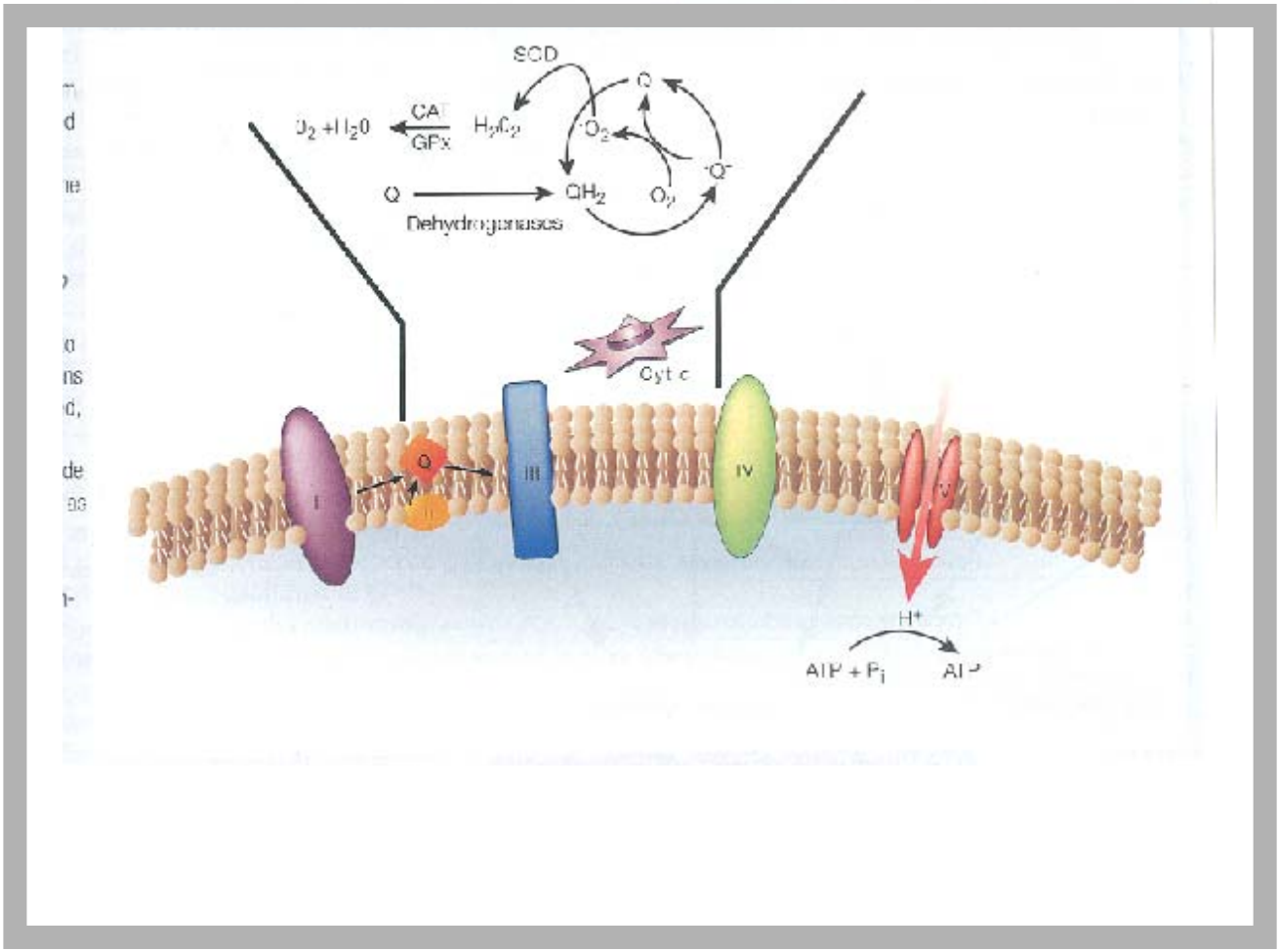
Multiples causes for aging and cancer



Aging mechanisms are risks for carcinogenesis

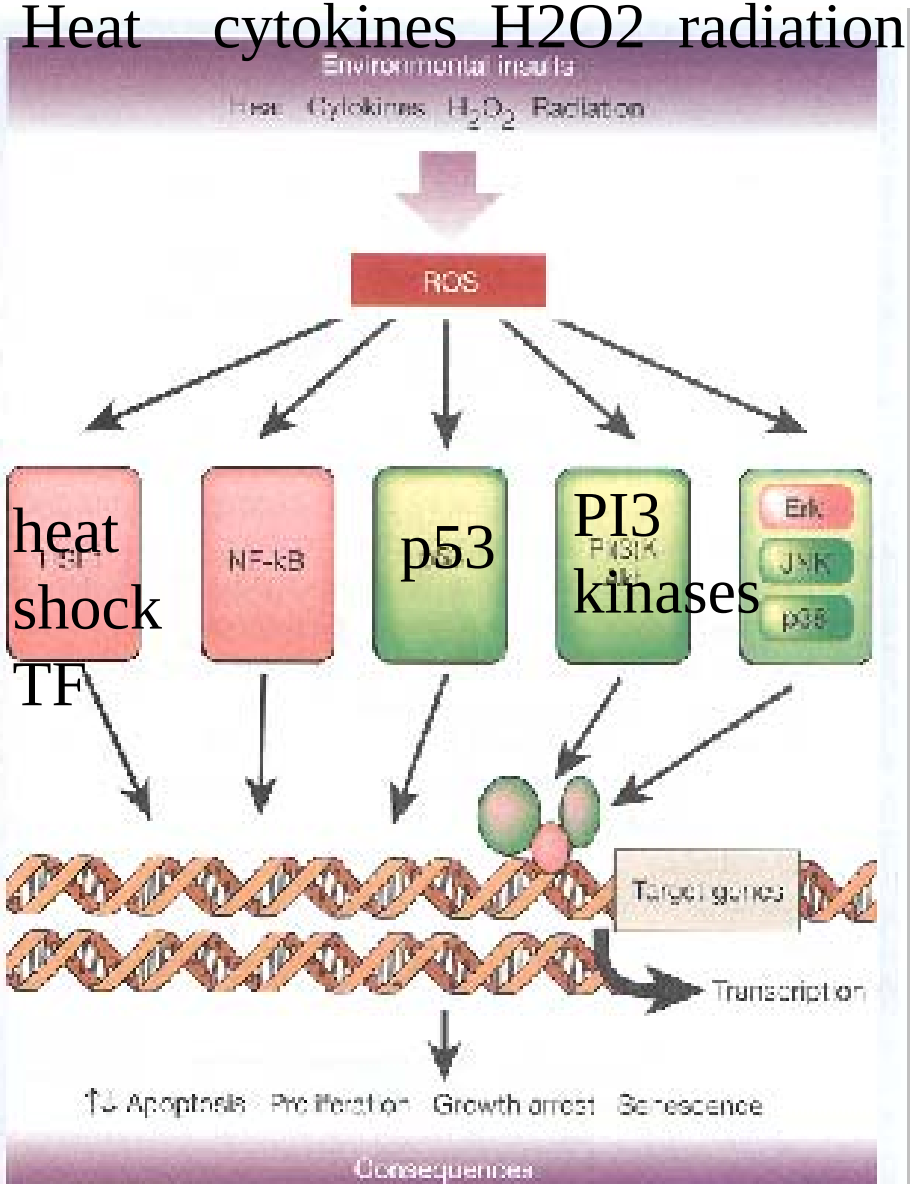


ROS production and accumulation of damage



Environmental risk factors

Heat cytokines H2O2 radiation



Accumulation of mutations in genes necessary for proliferation and repair

- Growth factors and their receptors
- Signal transduction pathway
- Cell cycle control genes
- DNA repair
- Tumor suppressors

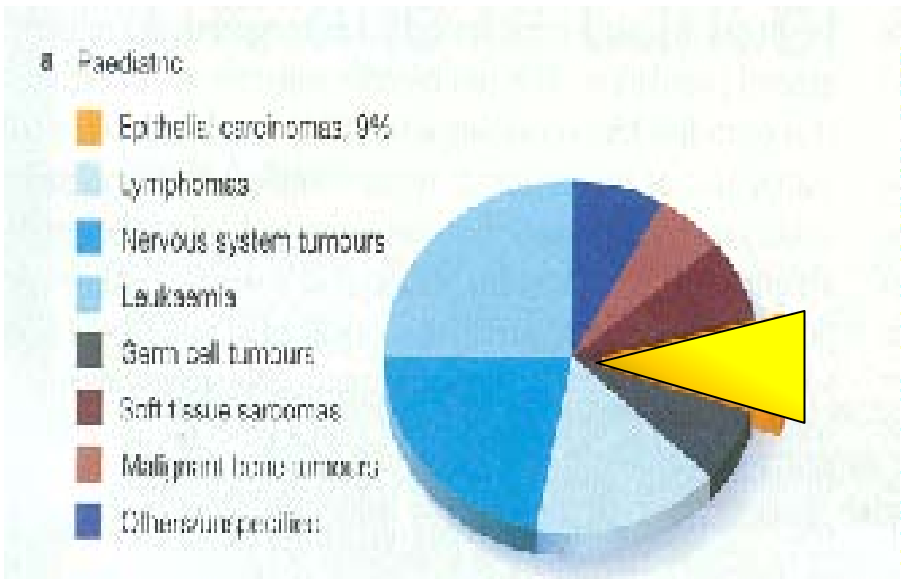
Epigenetic changes

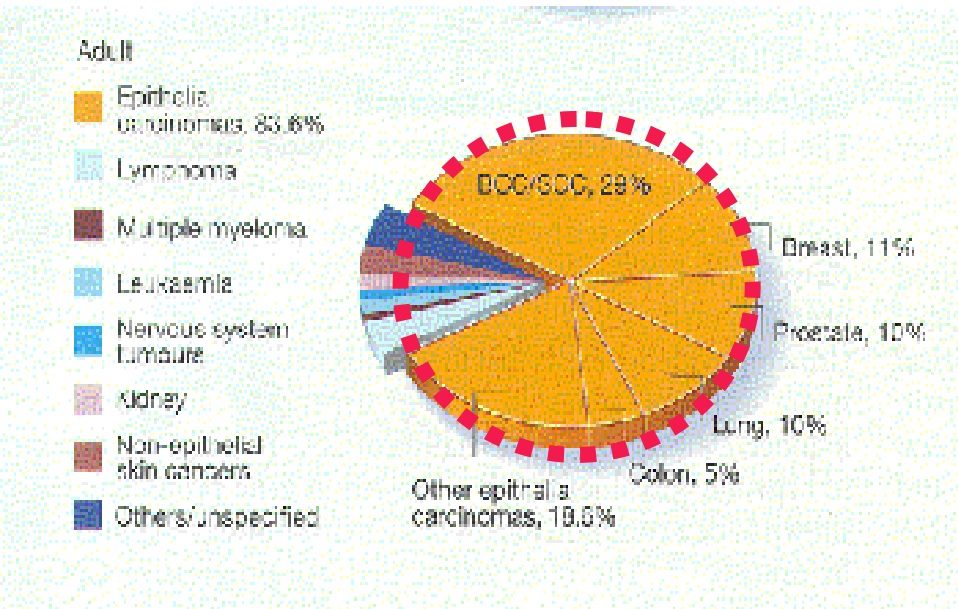
- Most prominent changes are methylation or phosphorylation of chromatin components – effecting gene expression
- Modification of chromatin structure leading to altered accessability of certain genes – silencing

What is silencing?

- Aging is triggered by a gradual erosion in silencing
- Global loss of silencing may result in a loss of a robust differentiated phenotype

Cancer in old age has a different face than cancer in young age.





BCC Basal cell carcinoma
SCC Squamous cell carcinoma

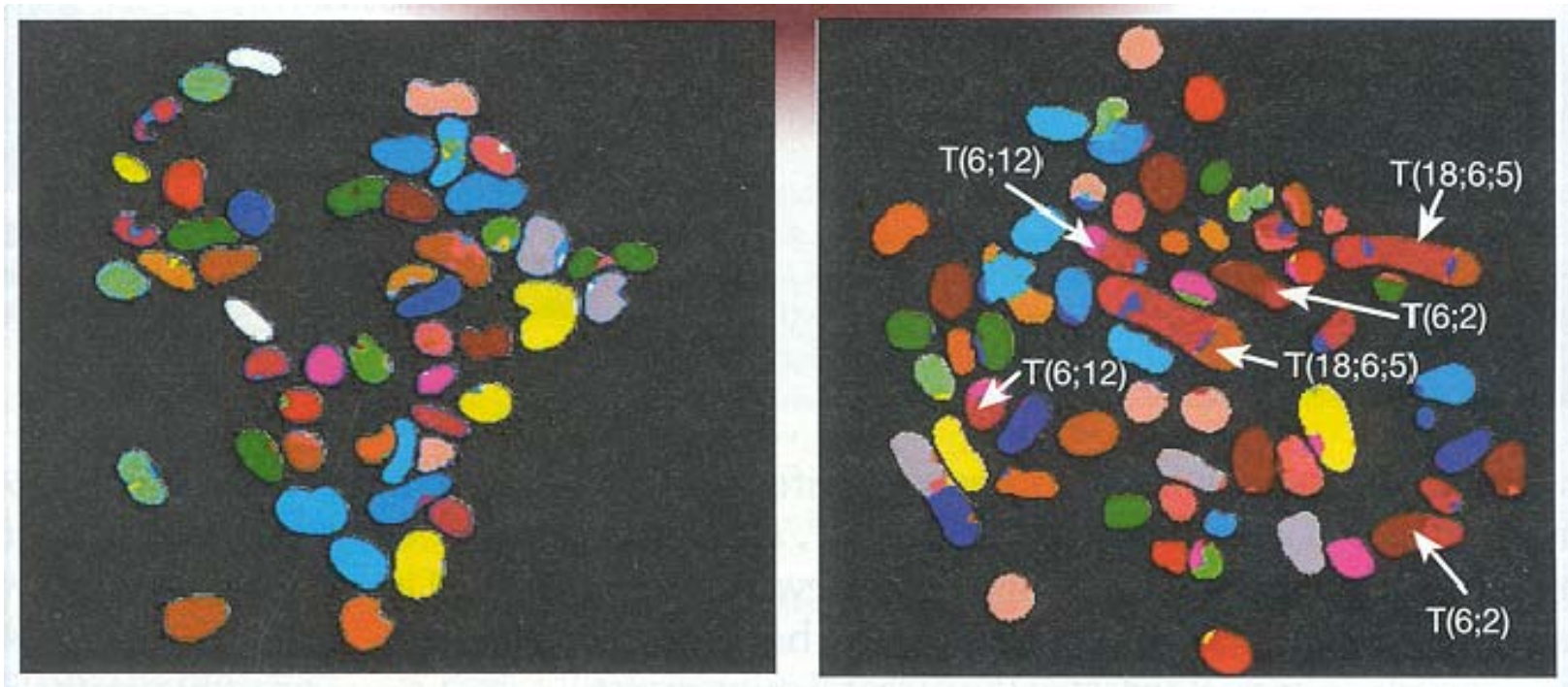
Why are
epithelial cell derived cancers
predominant in old age?

Characteristics of old age cancers

1. Derived from epithelial cells

2. Most tumors are highly genetically unstable

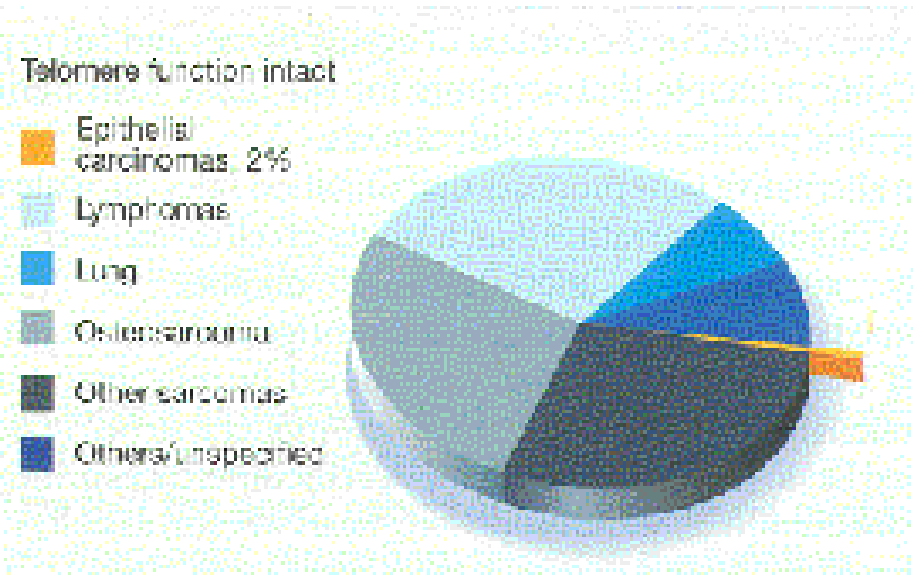
What is genetic instability?



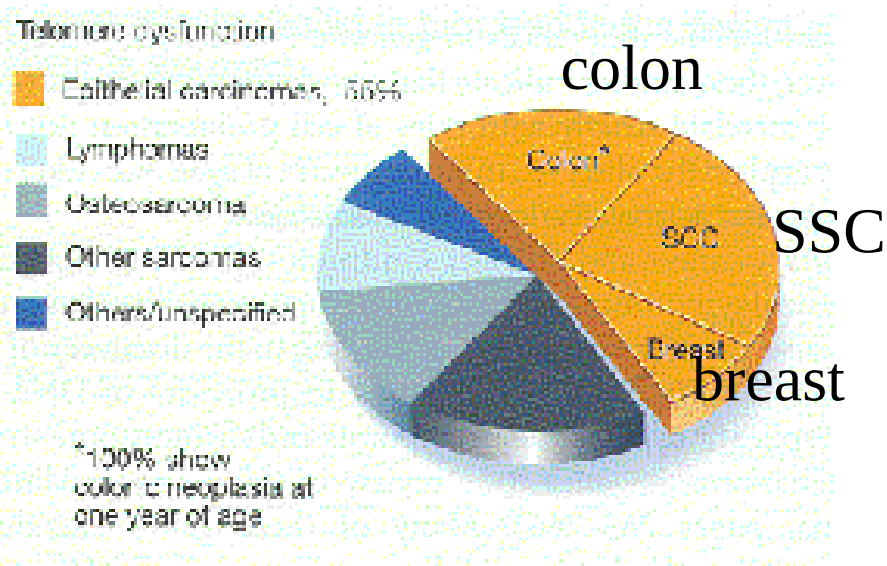
Spectral caryotype profile

Telomeres might be part of the story

Telomere function intact



Telomere disfunction

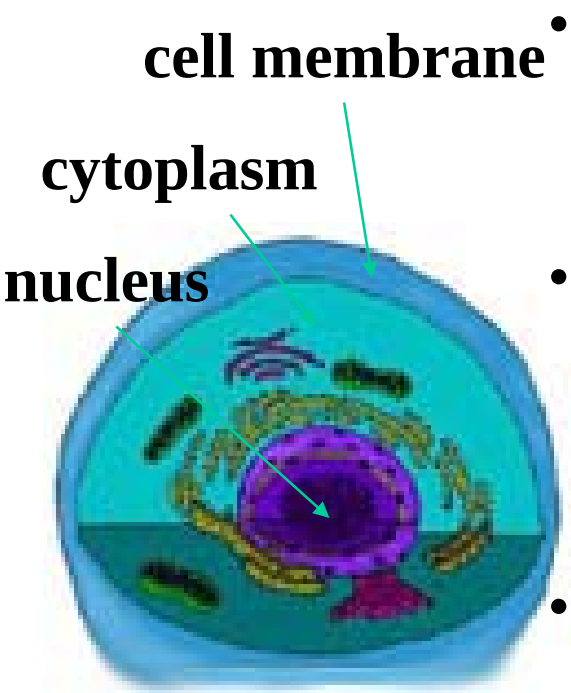


colon

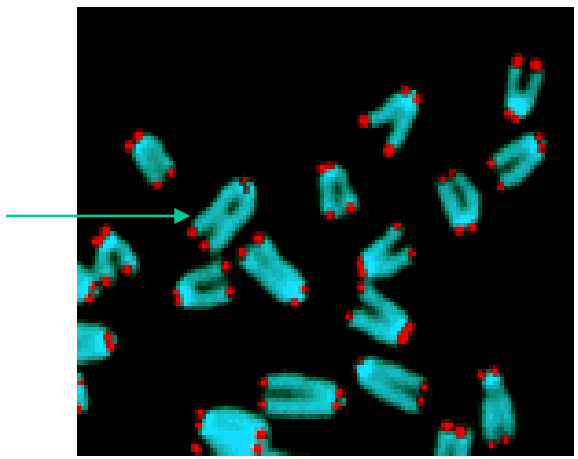
SSC

breast

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

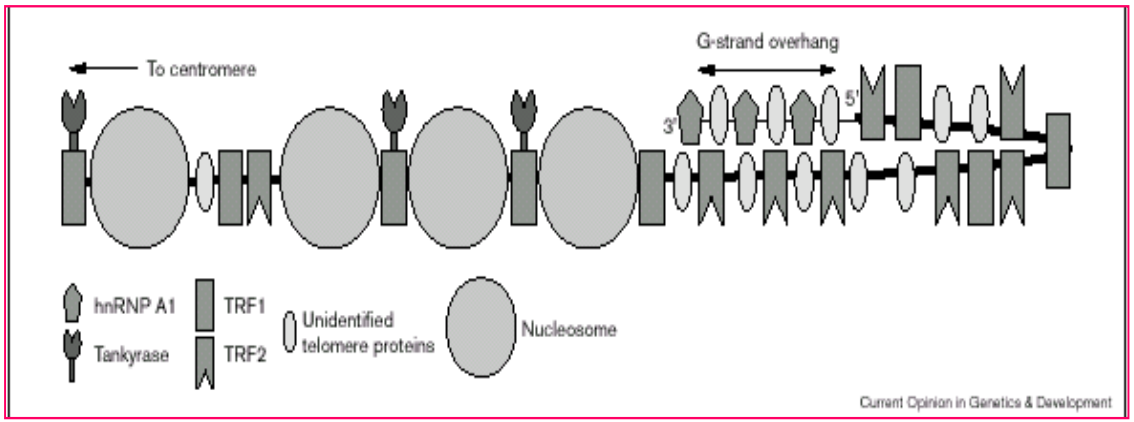
The theory of “replicative senescence”

- **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**

Telomere structure and function

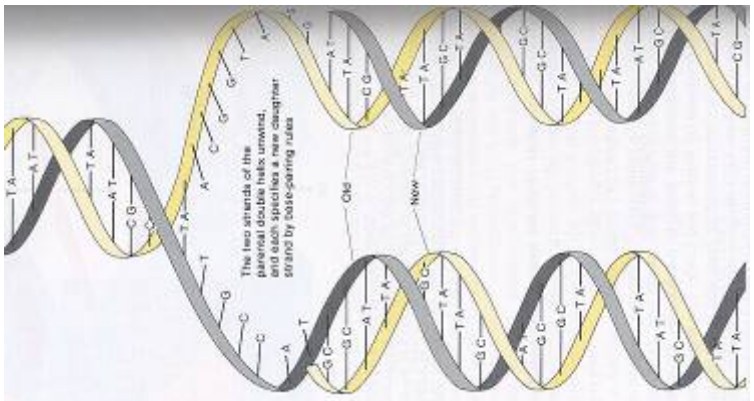


Telomere: a nucleoprotein complex

- **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

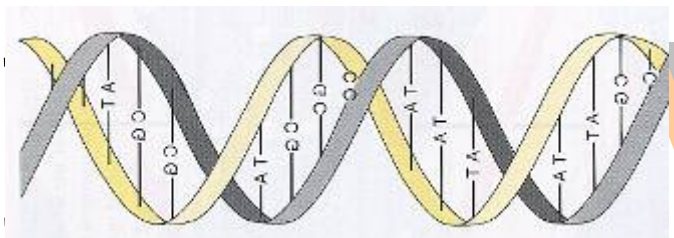


3’

5’

New synthesis RNA primer

The end replication problem



TTGGGGTTGGGGTTGGGGTT

G 3’

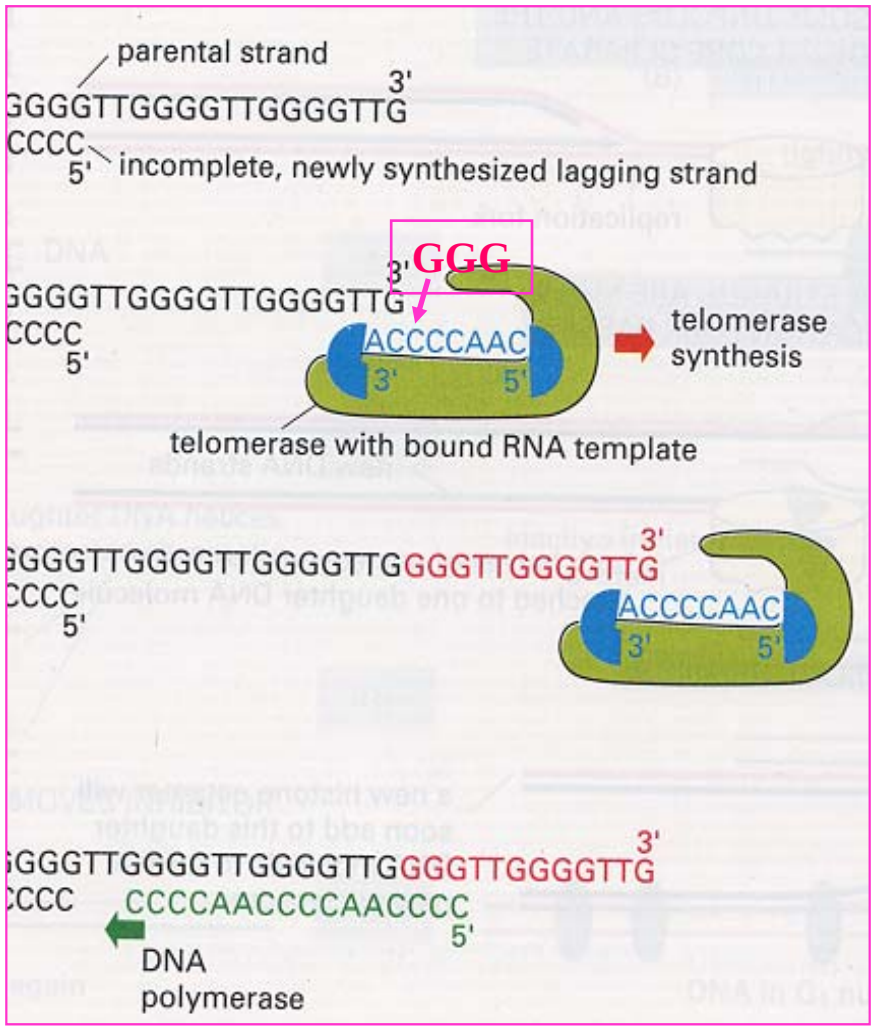
AACCCC 5’

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**



Limited expression of telomerase

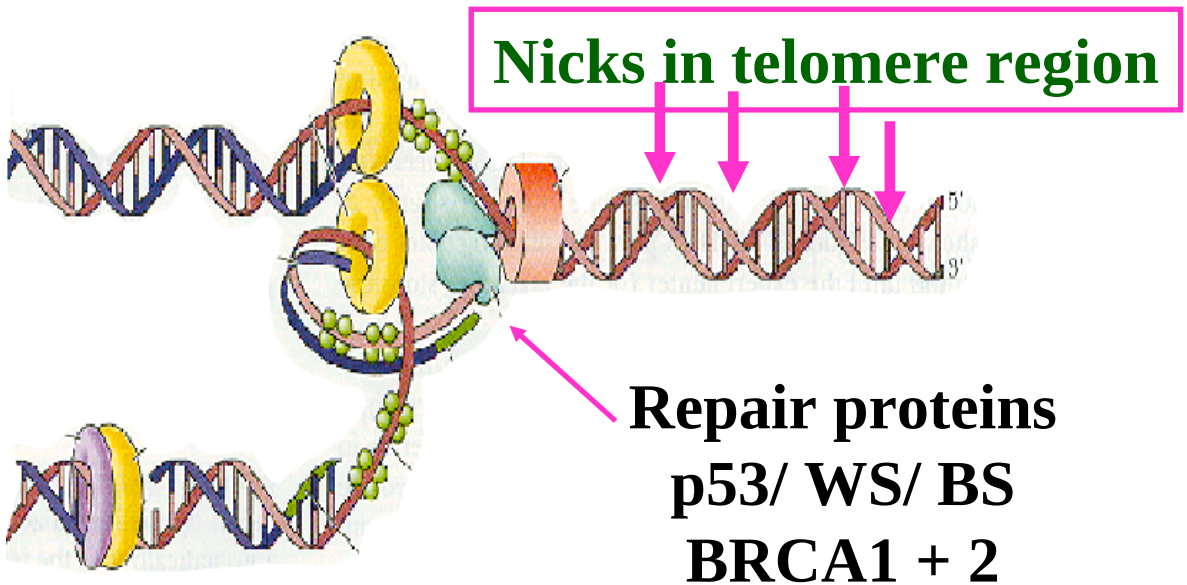
- **Telomerase is not expressed in normal somatic tissue**
- **Telomerase is expressed in the germline, in some highly proliferative stem cells, and in activated lymphocytes**
- **Telomerase is upregulated in cancer cells**

Seeking for immortality?

Stress induced telomere shortening

Accelerated aging

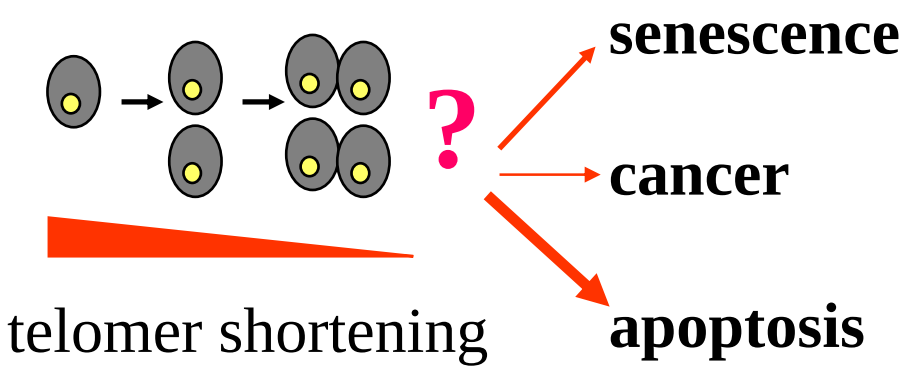
1. Cellular stress produces increased damage on telomere DNA



2. Defects in repair lead to accelerated loss of DNA fragments in telomere regions (Lansdorp, 2000)

Telomere length, cellular senescence, aging

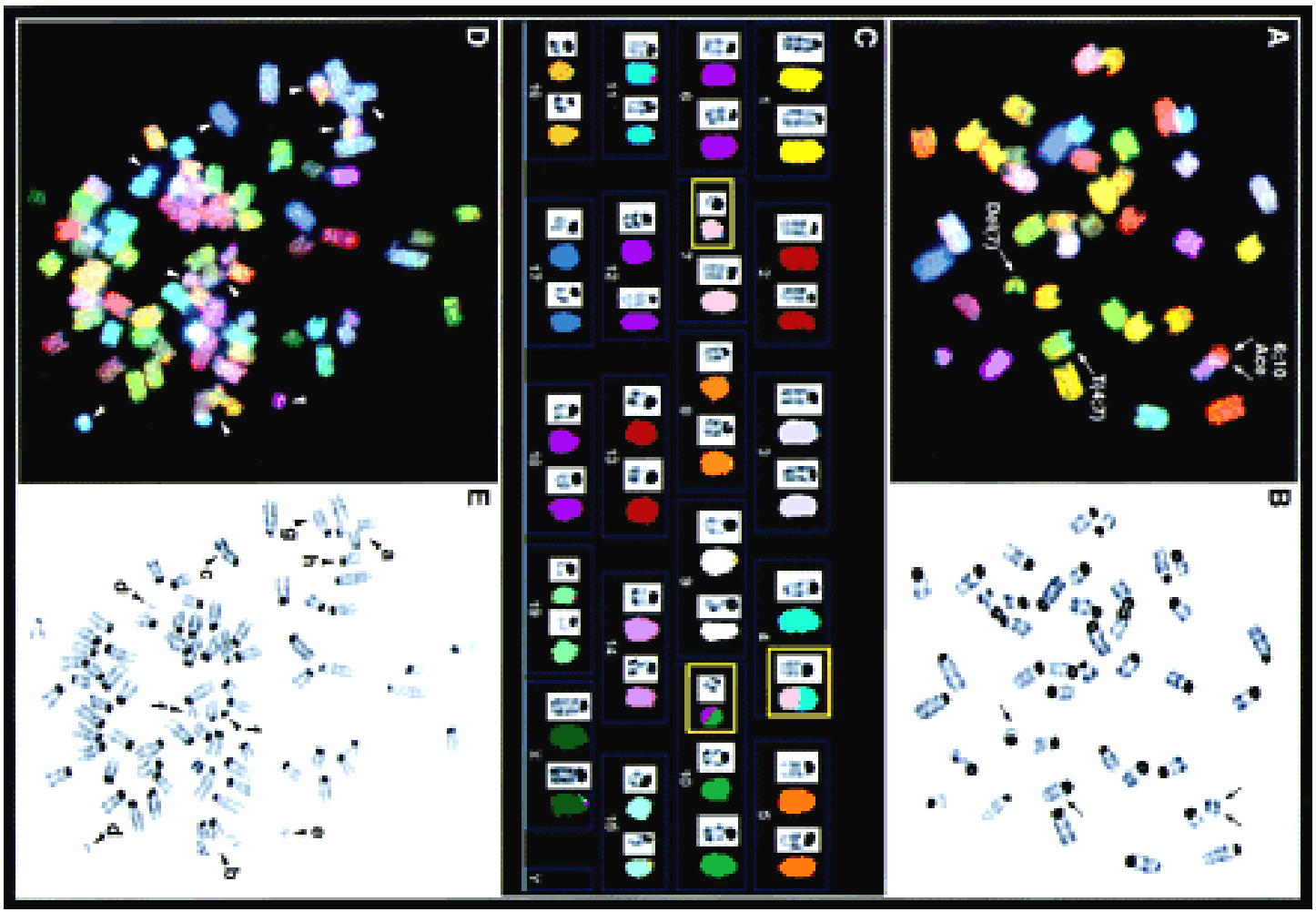
- **How telomere shortening is sensed is not known (telomere binding proteins?)**
- **Replication arrest can be overcome and result in genetic instability and cancer**
- **Accumulation of senescent cells and apoptosis contribute to the aging process**



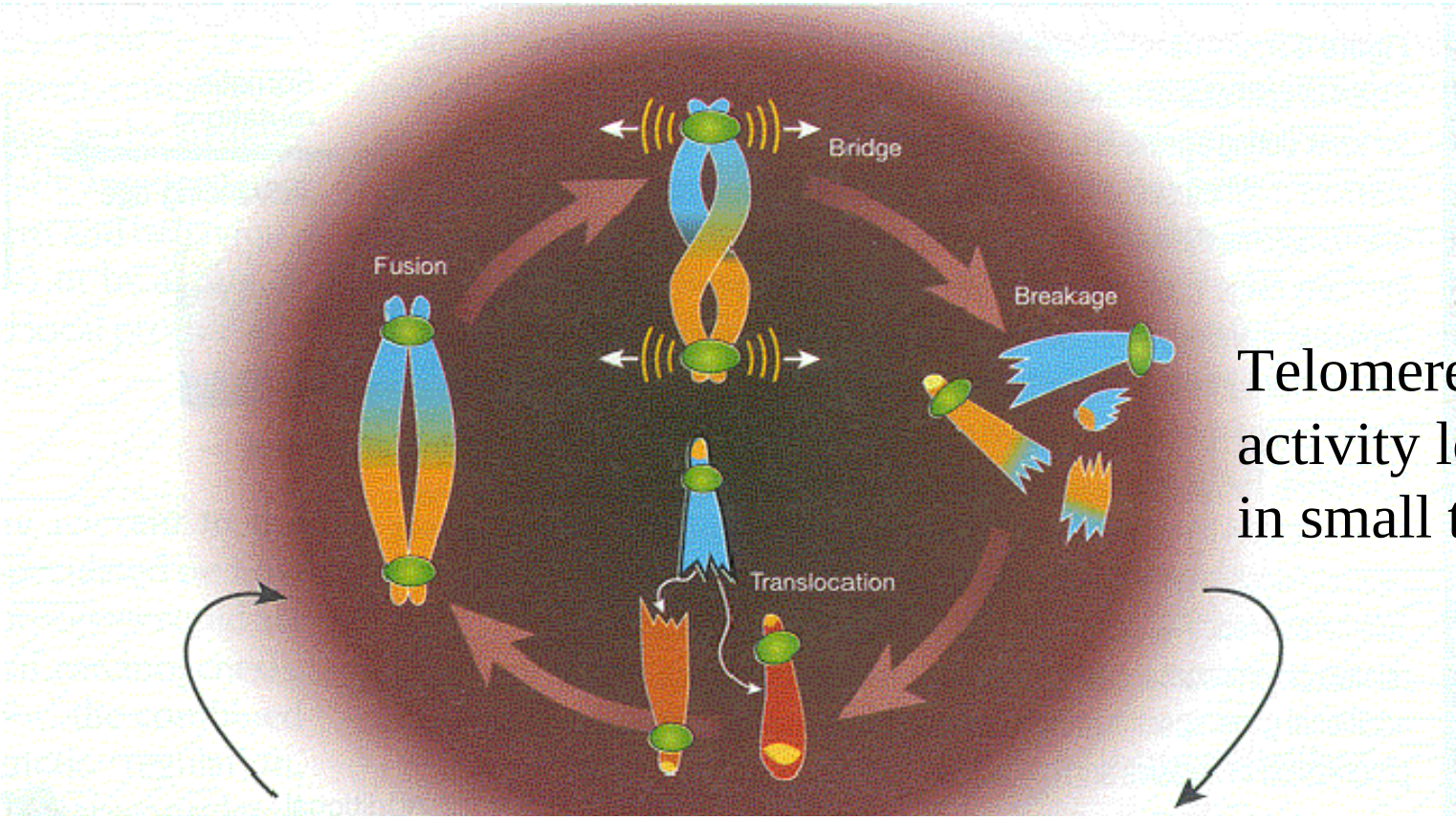
Mice deficient for telomerase

- 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
  - (Artandi et al. 2000)

Telomere shortening - loss of genetic stability



How can cancer evolve?



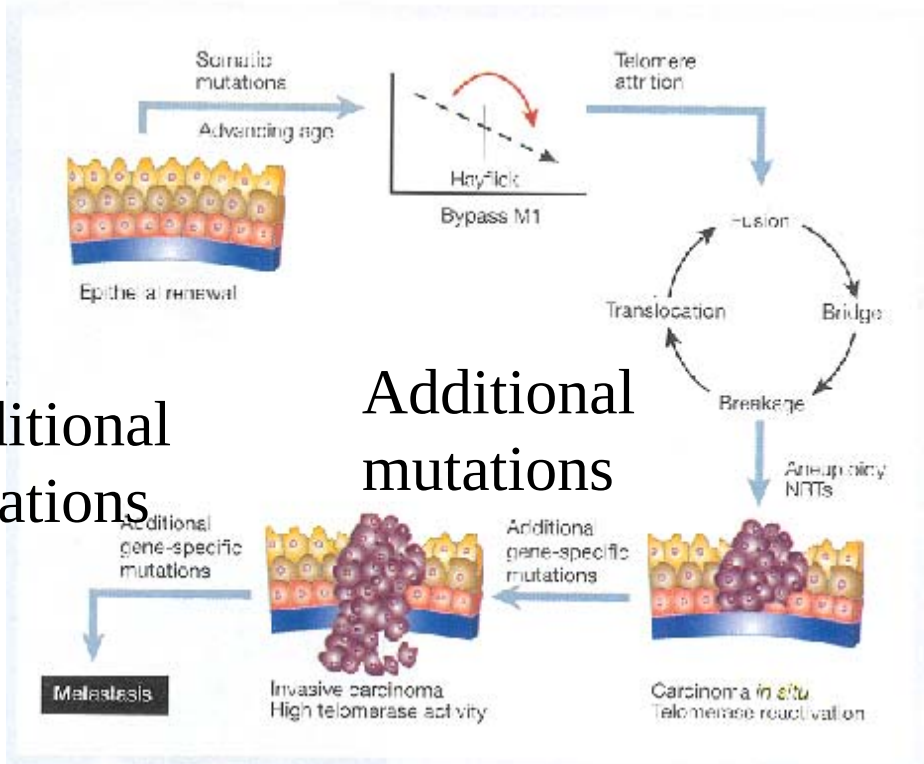
Telomere
activity low
in small tumors

Genetic instability
Telomeric instability

Why might telomeres be important in the old age cancers?

Somatic mutations

Telomere attrition

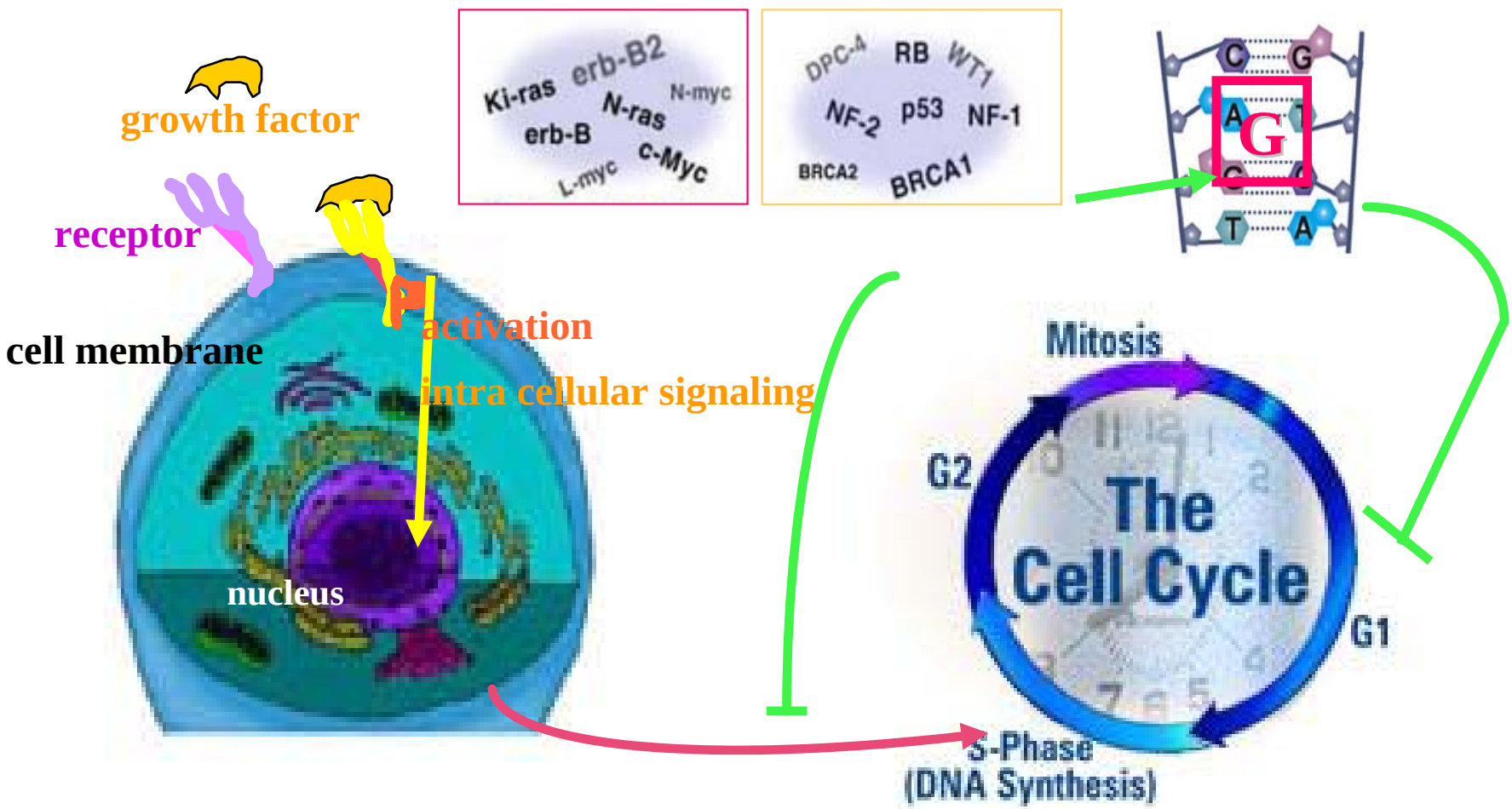


Additional mutations

Additional mutations

aneuploidy

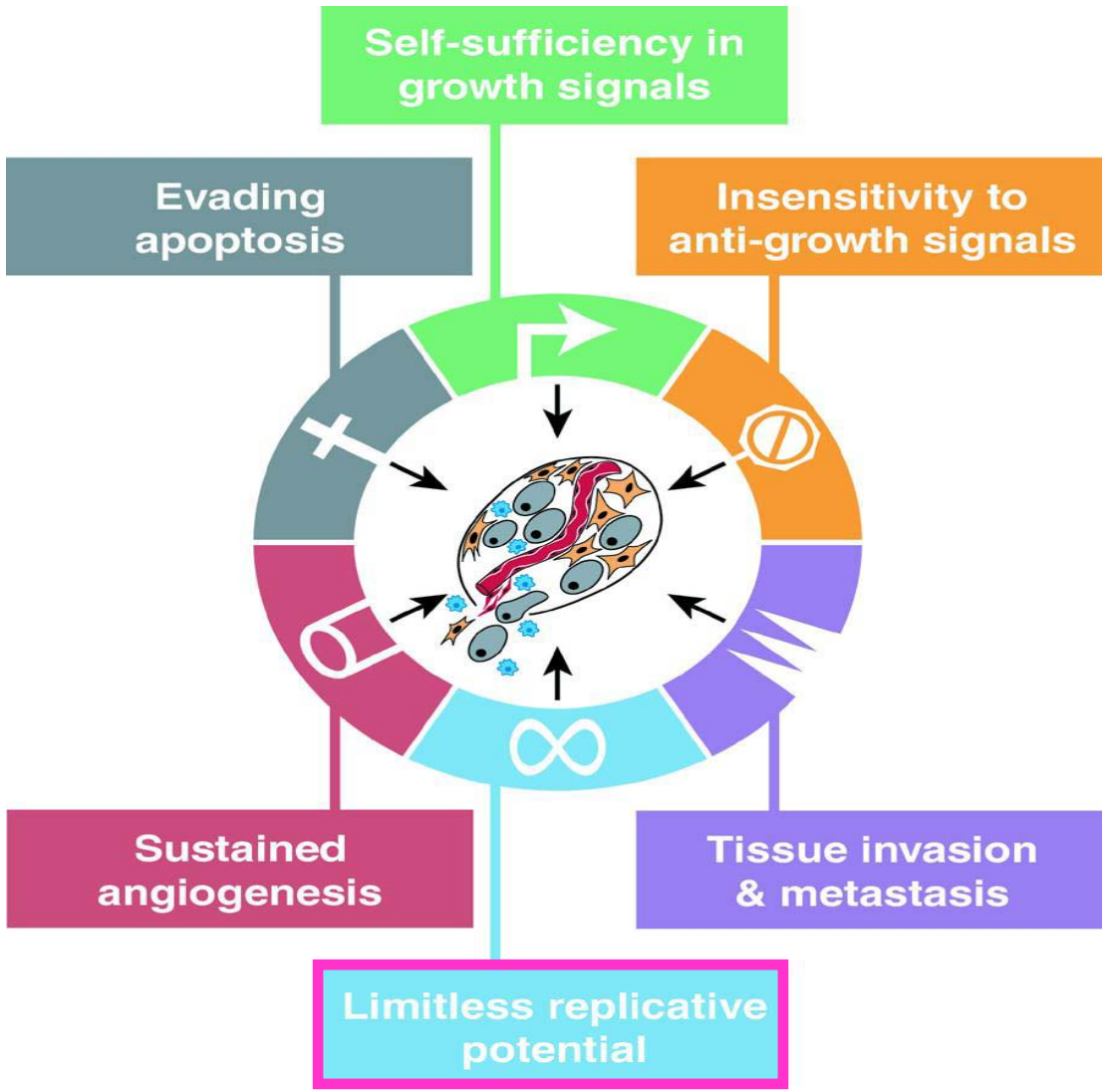
Suppression of genetic instability



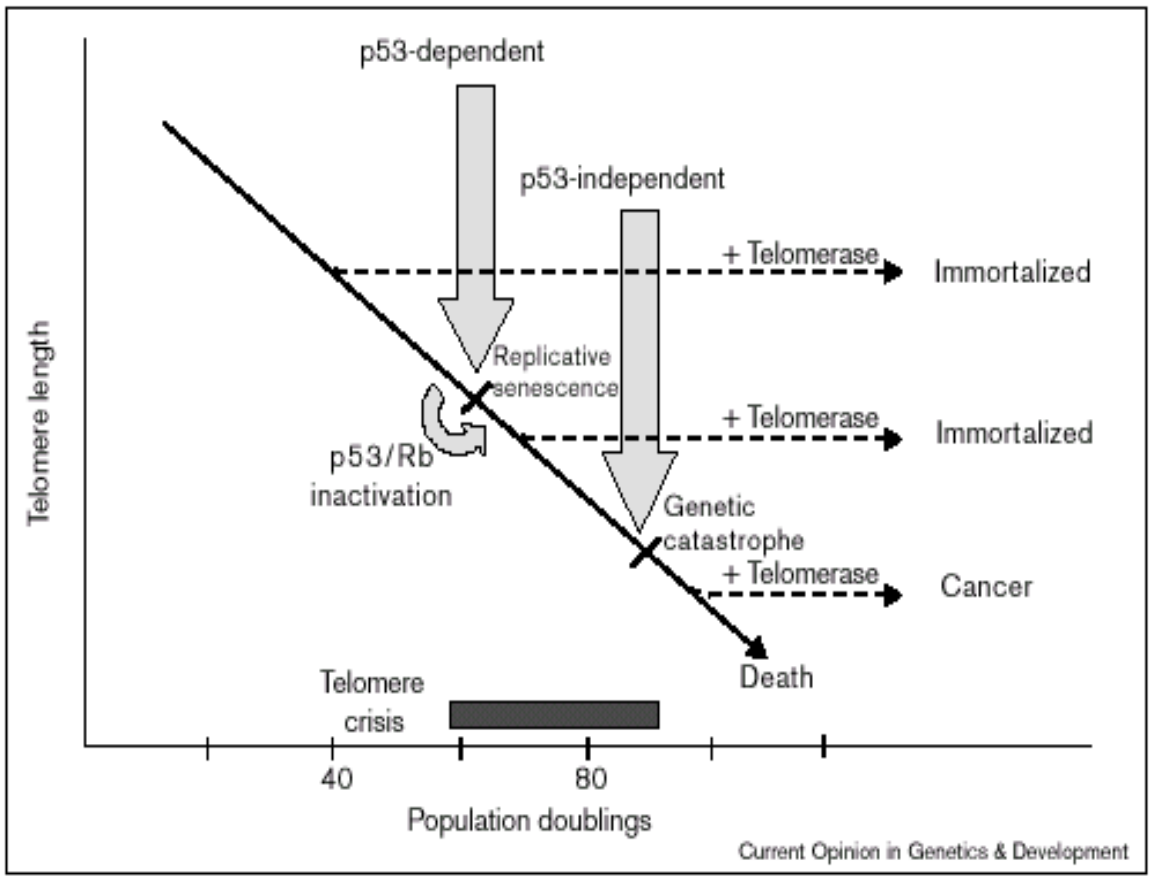
Loss of growth control: oncogene ↑

Loss of surveillance: anti-oncogene ↓
tumor suppressors

Multiple steps towards malignancy



Telomerase a double edged sword

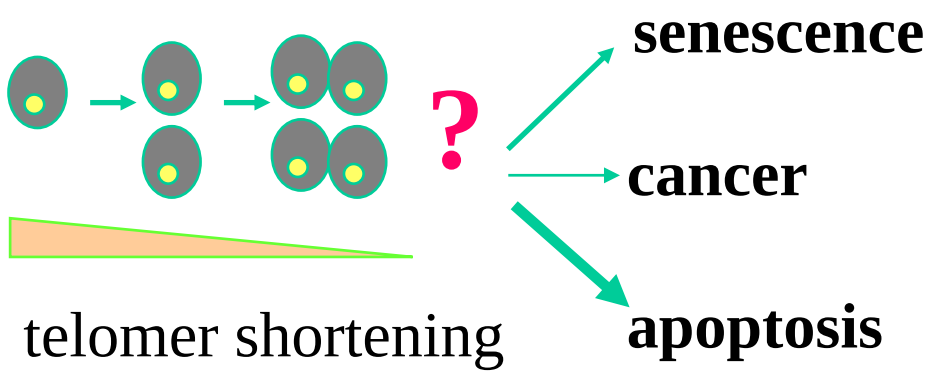


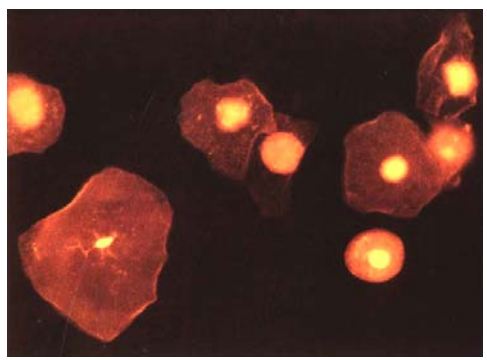
1. Activation of telomerase prior to genetic instability: immortality

2. Activation of telomerase after loss of growth control: immortality and cancer

Clinical impact of telomere length

- **Measuring telomere length: biological marker**
- **Measuring telomerase activity: tumor marker**
- **Inhibition of telomerase activity as specific anti-cancer therapy**
- **Upregulation of telomerase in cell therapy (hepatitis)**



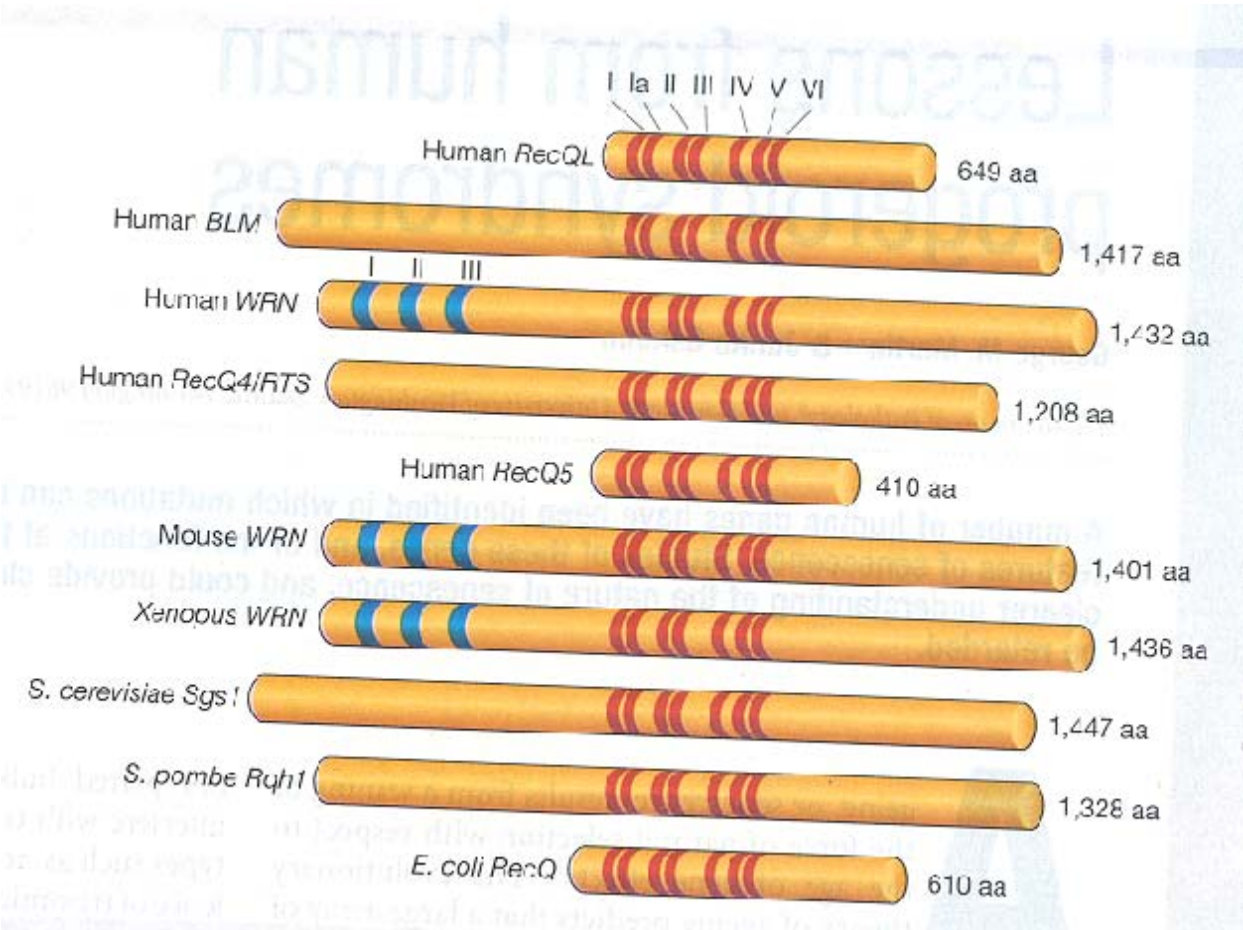


Determination of telomere length by quantitative FACS

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.**

Genes linked to premature aging syndromes



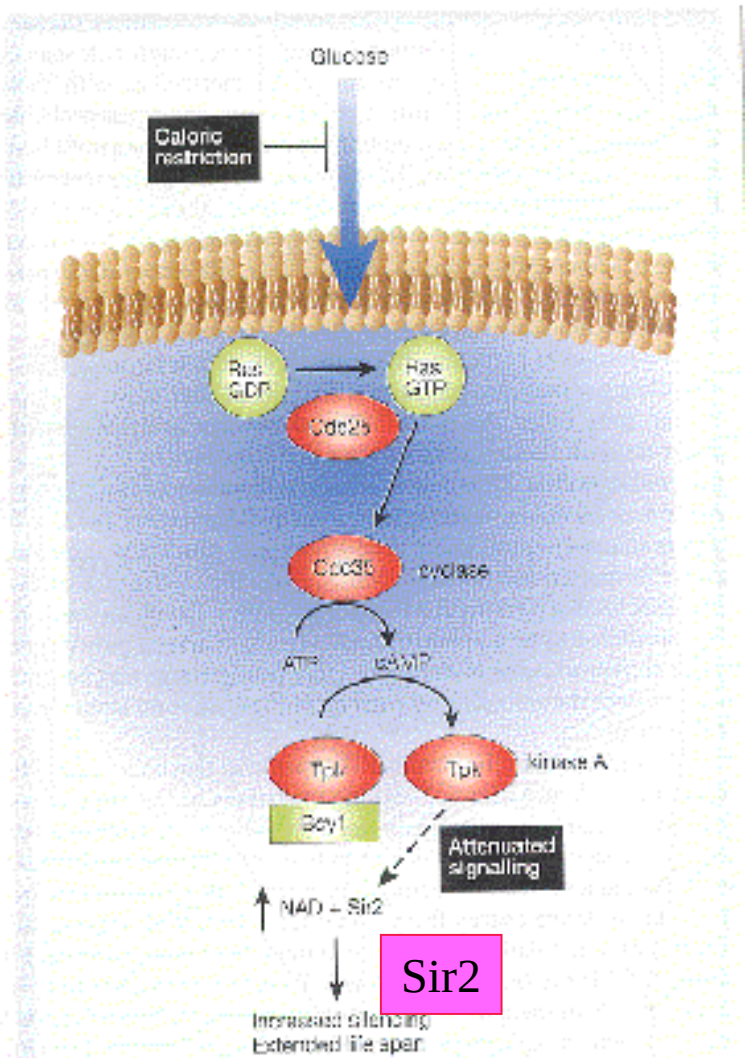
The link between telomeres and cancer

- Telomere erosion leads to telomeric instability
- Telomeric instability can potentiate the deleterious effect of mutations accumulated in « control genes »

Is there 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

Can we postpone or prevent the onset of cancer?



Caloric restriction

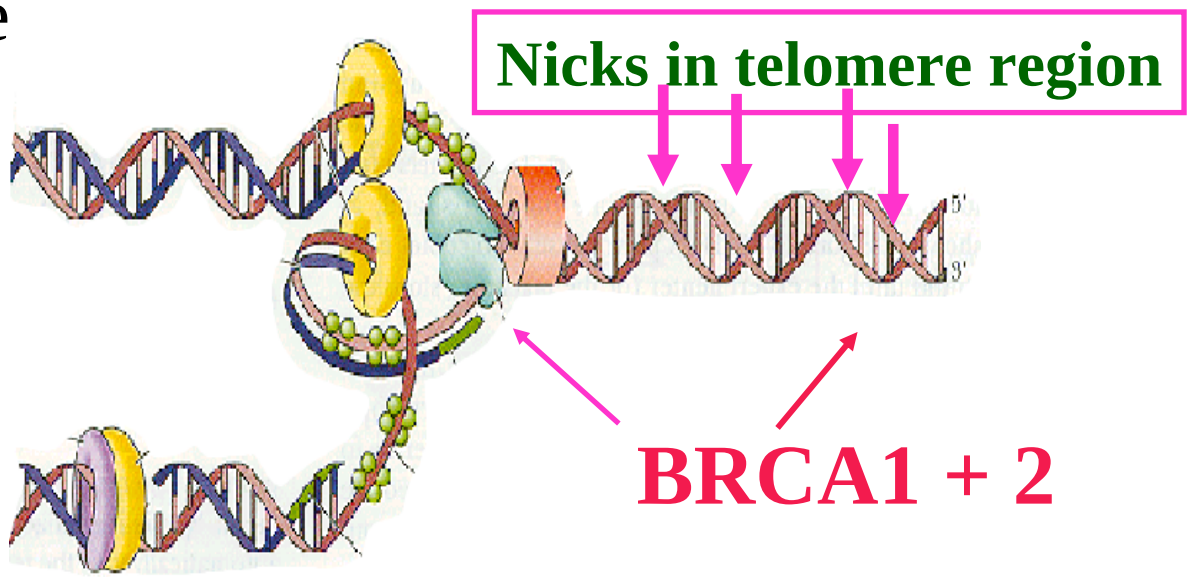
Intracellular signaling

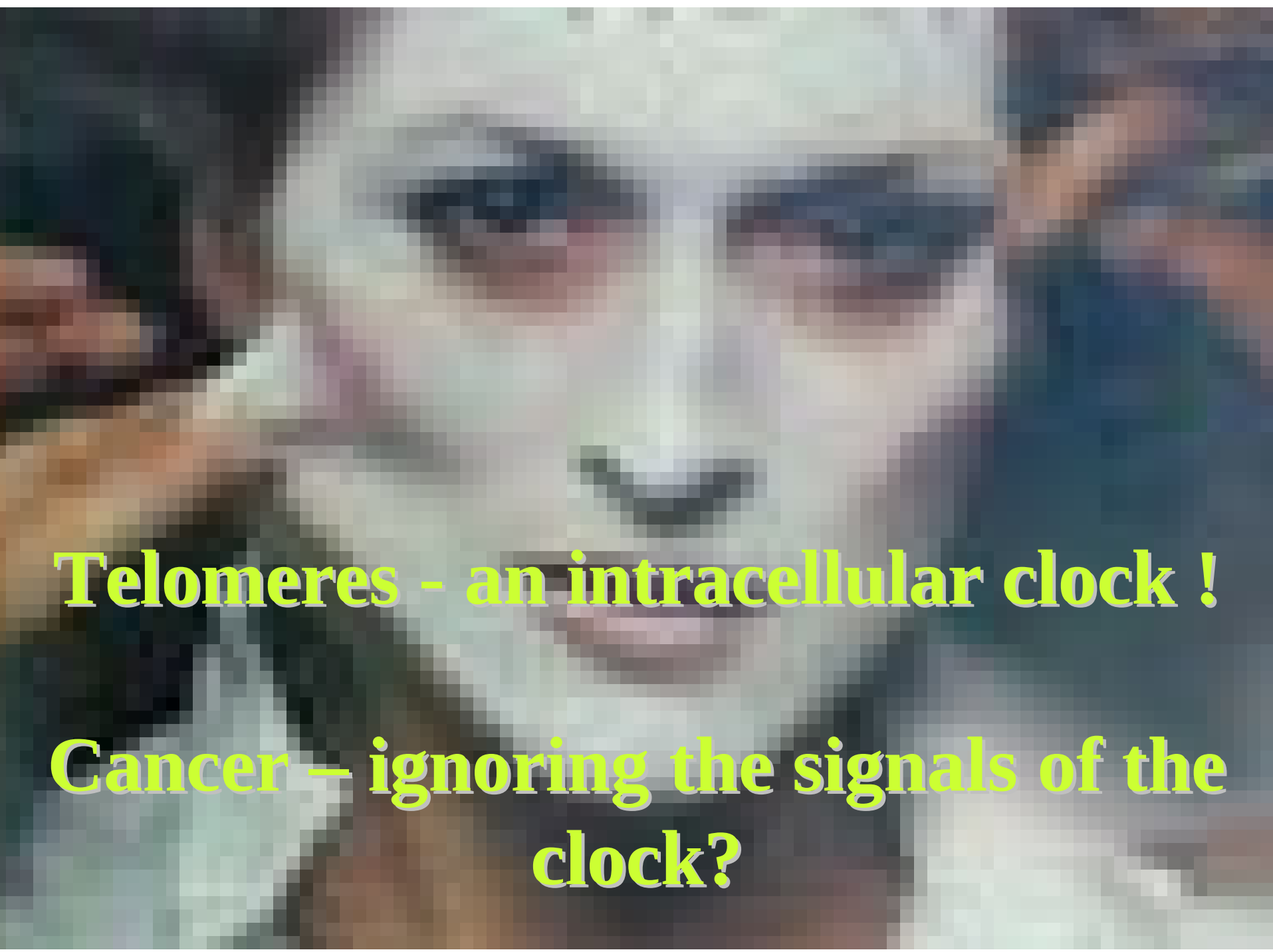
Reduced silencing
(altered gene expression)

Sir2 is increasing silencing

The cancer predisposition genes

- BRCA1 and 2 (breast cancer predisposition gene)
  - Deficiency of BRCA1/2 – genetic instability
  - Function DNA repair in complex with other repair proteins: BRCA2, ATM, Rad51, helicases
- New function of BRCA2: protection of telomere structure




Telomeres - an intracellular clock !
Cancer – ignoring the signals of the clock?