

# GENOMIC INSTABILITY AS A LINK BETWEEN CANCER AND AGING

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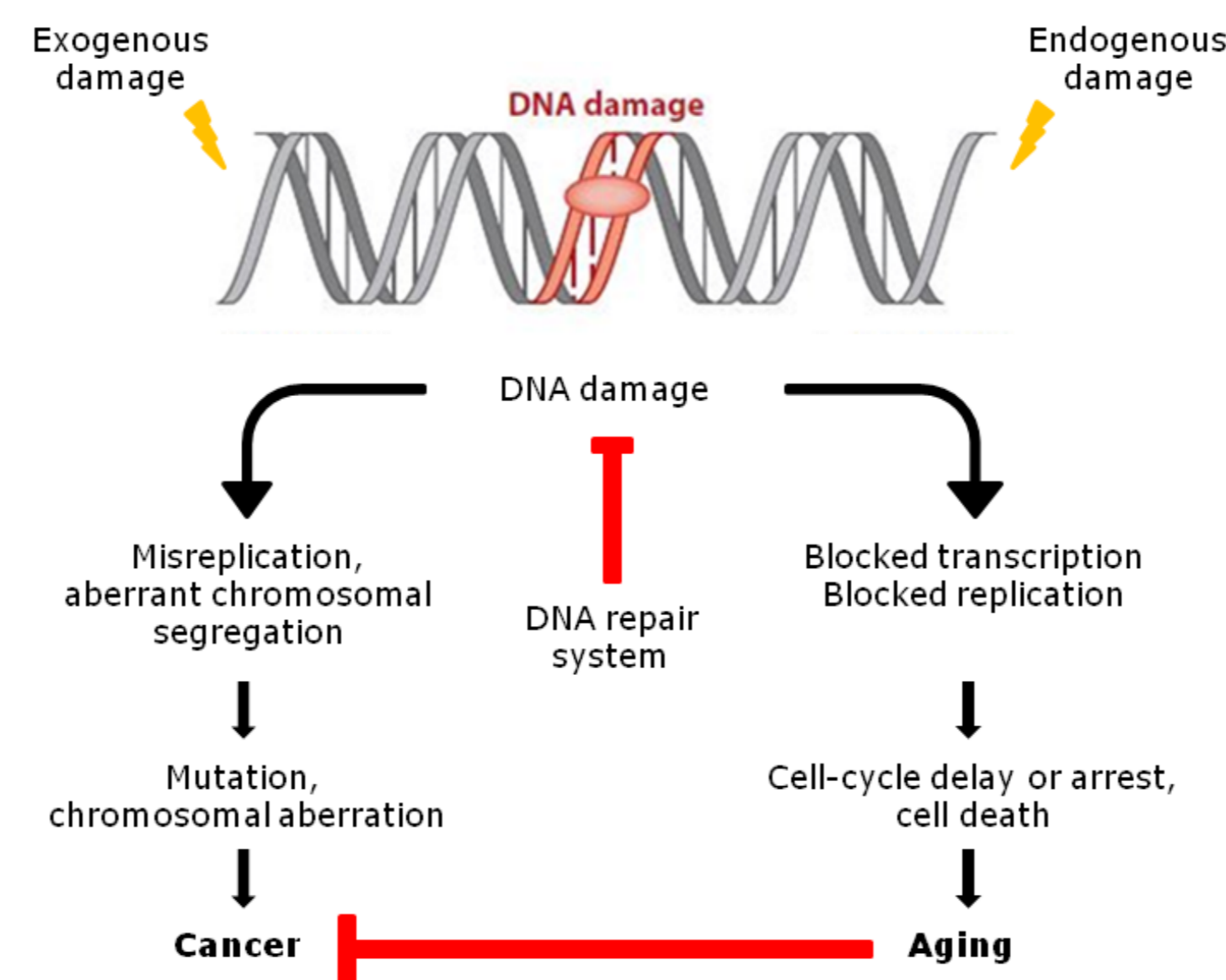
## WHAT IS GENOMIC INSTABILITY?

Genomic instability is the natural tendency of genomes to undergo alterations under physiological conditions. It refers to an elevated spontaneous or induced mutation rate in cells.

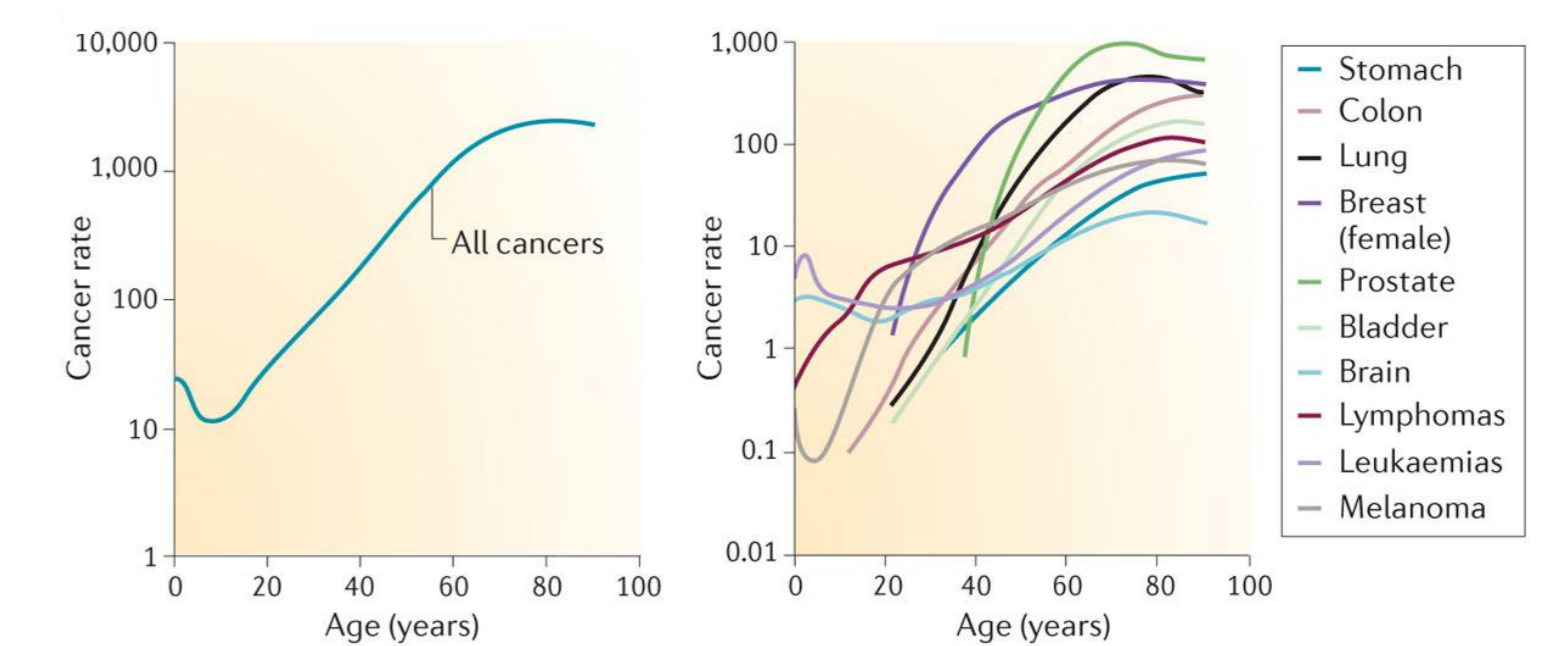
Genomic instability is considered a key endogenous mechanism for accumulation of mutations, and therefore, it has been proposed as an engine of tumorigenesis.



- Chromosomal instability (CIN)
- Microsatellite instability (MSI)



Changes can arise spontaneously during the basic processes of cellular metabolism due to DNA repair errors, recombination and replication errors or due to the action of metabolic intermediates with reactive capacity.



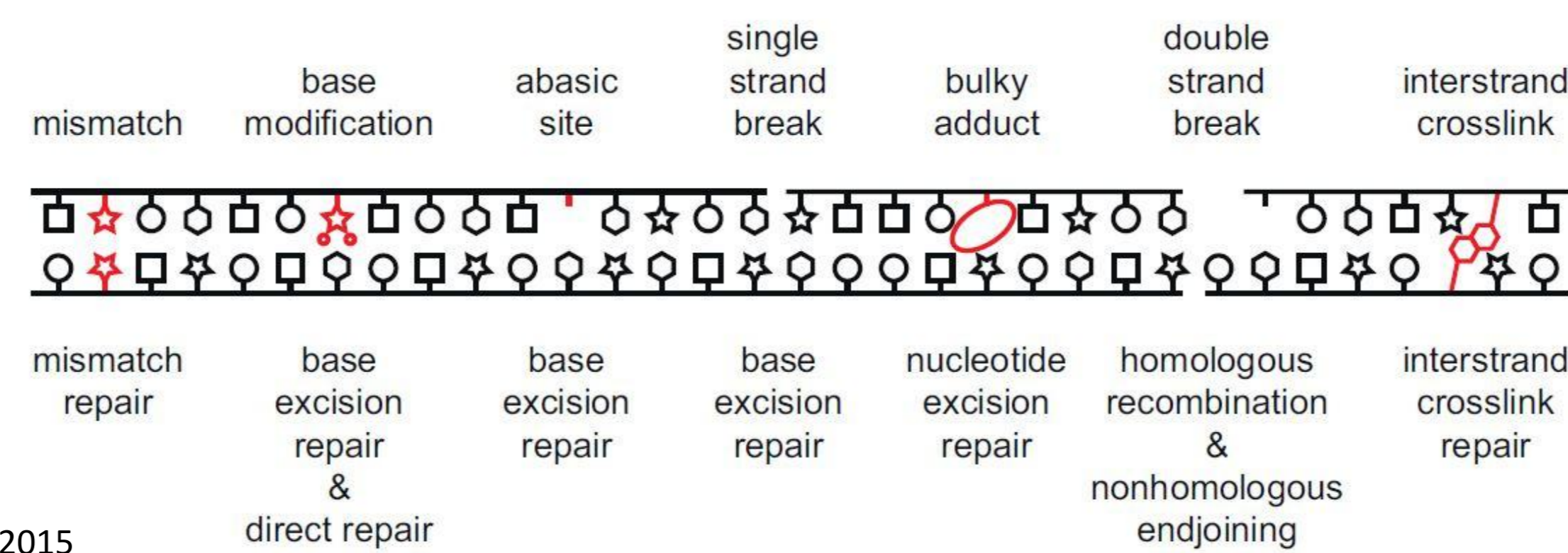
de Magalhães, J.P., 2013

## DNA DAMAGE REPAIR PATHWAYS

Genome stability is crucial both to maintain cellular homeostasis as to ensure genetic continuity during cell proliferation and reproduction of multicellular organisms.

Genome maintenance also includes a complex telomere-processing machinery and guards the integrity of mitochondrial DNA.

Burkhalter, M.D., 2015



The main role of DNA repair is to allow the genetic information to be replicated faithfully and to be transcribed efficiently. Some types of damage escape detection by repair pathways and the lesions may accumulate.

There are some human genetic diseases caused by the alteration of various genes involved in repair mechanisms (e.g. xeroderma pigmentosum, Cockayne syndrome, Fanconi anemia).

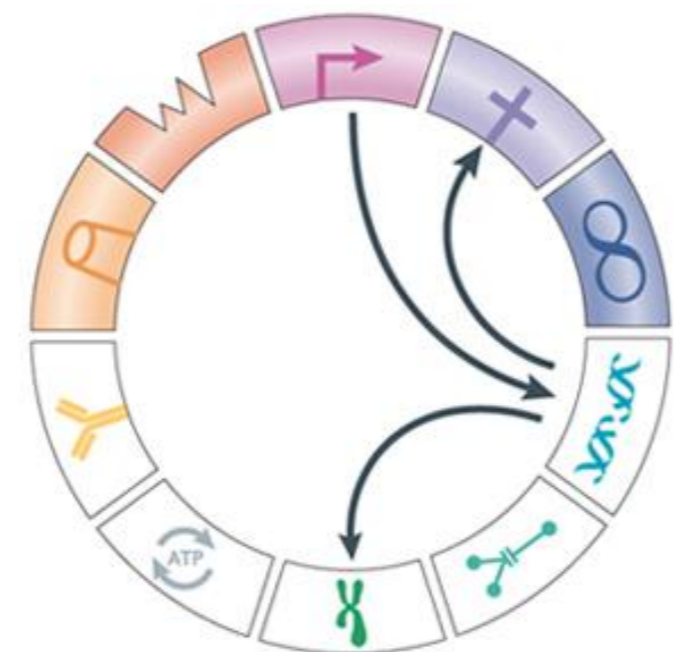
## GENOMIC INSTABILITY IN CANCER

Any cell to become a cancer cell has to acquire a list of competences being genome instability one of the new generation hallmarks. Genomic instability of tumors is related to mutations in some or many DNA repair genes so that increases the probability to accumulate mutations.

Hereditary cancers



Sporadic cancers



Negrini, S., 2010

Cancer stem cells with genetic instability can be considered as 'the best vehicle with the best engine' for tumor progression because they preserve its stemness capacity giving rise to all cell types found in tumors.

Telomerase loss generates karyotype instability, amplification and deletion of chromosomal fragments. It exists a balance between healthy and disease and it is closely related with telomere length.

## GENOMIC INSTABILITY IN AGING

Genomic instability happens during normal aging and its increase must accelerate aging and contrary, its decrease must delay the age-related signs, increasing the lifespan.

Aging triggers progressively the activation of *INK4a/ARF* locus which also induces senescence.

In aged organisms, the cellular replacement system (removing senescent cells) may become ineffective or can deplete the regenerative capacity of stem cells, producing the accumulation of senescent cells and the loss of tissue homeostasis that can contribute to aging.



López-Otín, C., 2013

Long telomeres  
Low *INK4a*  
Low DNA damage



Short telomeres  
High *INK4a*  
High DNA damage

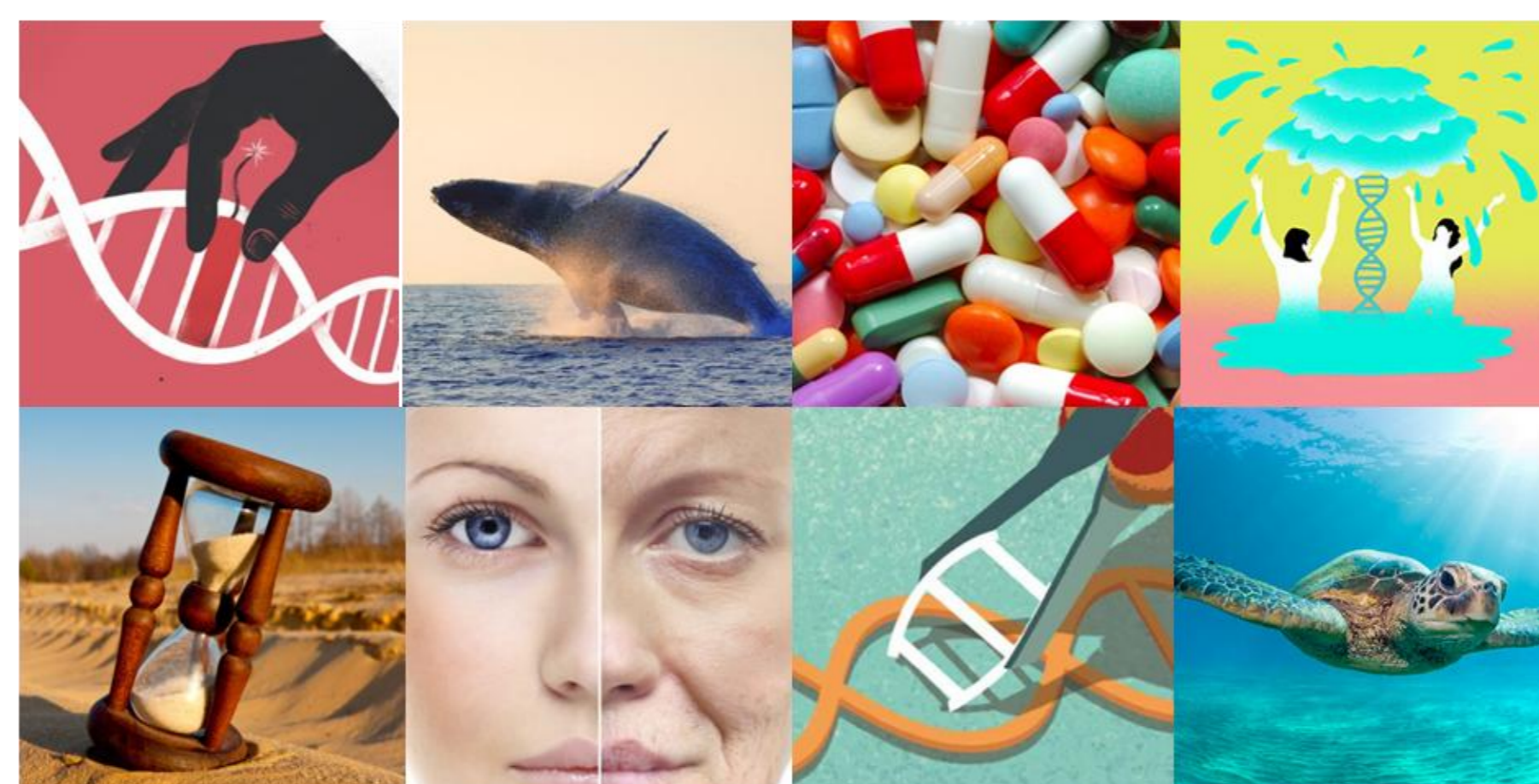
## FUTURE PERSPECTIVES

➤ Create stem cells and mice models of genomic instability generated by CRISPR/Cas9 technology introducing DBSs or single-nucleotide changes into the genome mimicking human tumors.

➤ Develop specific cancer chemoprevention to provide anti-cancer and anti-aging benefits using natural, synthetic or biological agents to delay initial steps of aging and to decrease the risk of inherited cancer.

➤ Study of cancer and aging resistant animal models.

- Identify genes that protect against cancer from long-lived organisms (*C.elegans*, turtles, naked-mole rats, bowhead whale) by GWAS.
- Understand genes and processes used to protect facing cancer and aging.



➤ Try to identify the genetic factors responsible for the derepression of the *INK4a/ARF* locus during cancer and aging through functional genomics and epigenomics in single-cell analysis.

➤ Gene therapy as an approach to combat aging delivering telomerase (TERT) using viral vectors.

➤ Analyze the transcriptome under basal p53 conditions because of its relevance for aging protection.

➤ Improve computational analysis of genome-wide sequencing data of DNA damage sites and generate tools to analyze huge amounts of data sets of tumor genomes from several consortia as The Cancer Genome Atlas (NIH).

## CONCLUSIONS

➤ Face cancer as a chronic disease enabling a long-term management of the disease. Metastatic patients cannot be cured but can be controlled over the time.

➤ Despite the fact that the underlying mechanisms that link cancer and aging are largely unknown, these remarkable cellular events are two sides of the DNA-damage problem.

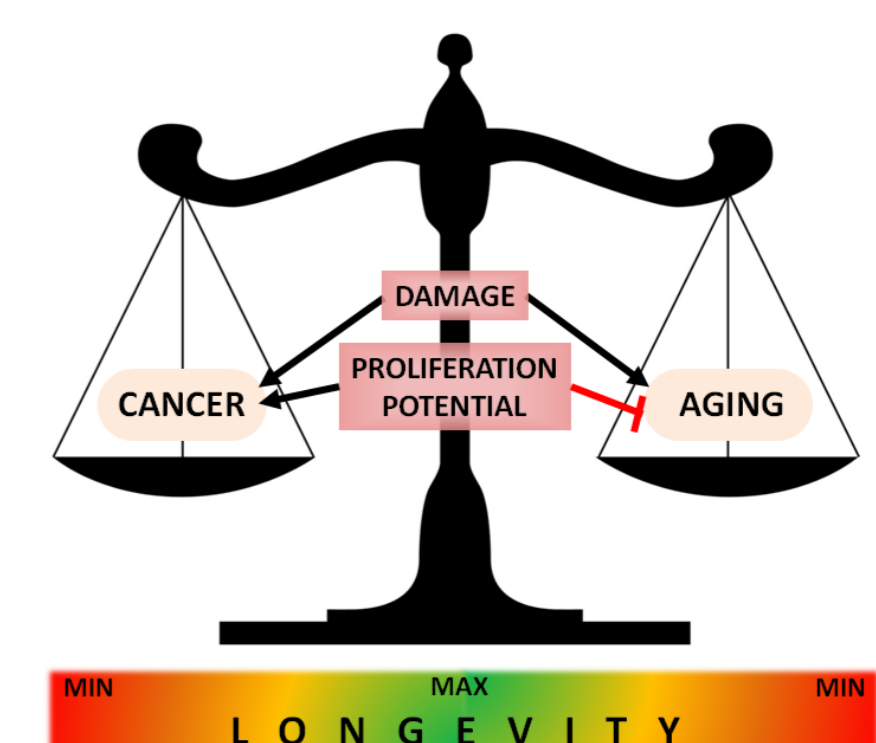
➤ Genomic instability plays a crucial role in the regulation of age-related diseases and also in aging process.

➤ DNA damage and mainly genomic instability trigger the deregulated events in cancer, showing some of the differences between hereditary and sporadic cancers.

➤ Genomic instability drives human genome evolution, both in healthy and disease states.

➤ There are still no answers that explain what drives initial genomic instability and its continued progression.

➤ Is genome instability a cause or a consequence?



TWO SIDES OF THE DNA-DAMAGE PROBLEM

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