Los 9 sellos del paso de los años

The Hallmarks of Aging
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The Hallmarks of Aging

Una introducción necesaria

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The Hallmarks of Aging

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Abstract

Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. This deterioration is the primary risk factor for major human pathologies including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Aging research has experienced an unprecedented advance over recent years, particularly with the discovery that the rate of aging is controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution. This review enumerates nine tentative hallmarks that represent common denominators of aging in different organisms, with special emphasis on mammalian aging. These hallmarks are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. A major challenge is to dissect the interconnectedness between the candidate hallmarks and their relative contribution to aging, with the final goal of identifying pharmaceutical targets to improve human health during aging with minimal side-effects.

Keywords

aging; cancer; DNA damage; epigenetic; healthspan; lifespan; longevity; metabolism; mitochondria; nutrient-signaling pathways; senescence; stem cells; telomeres

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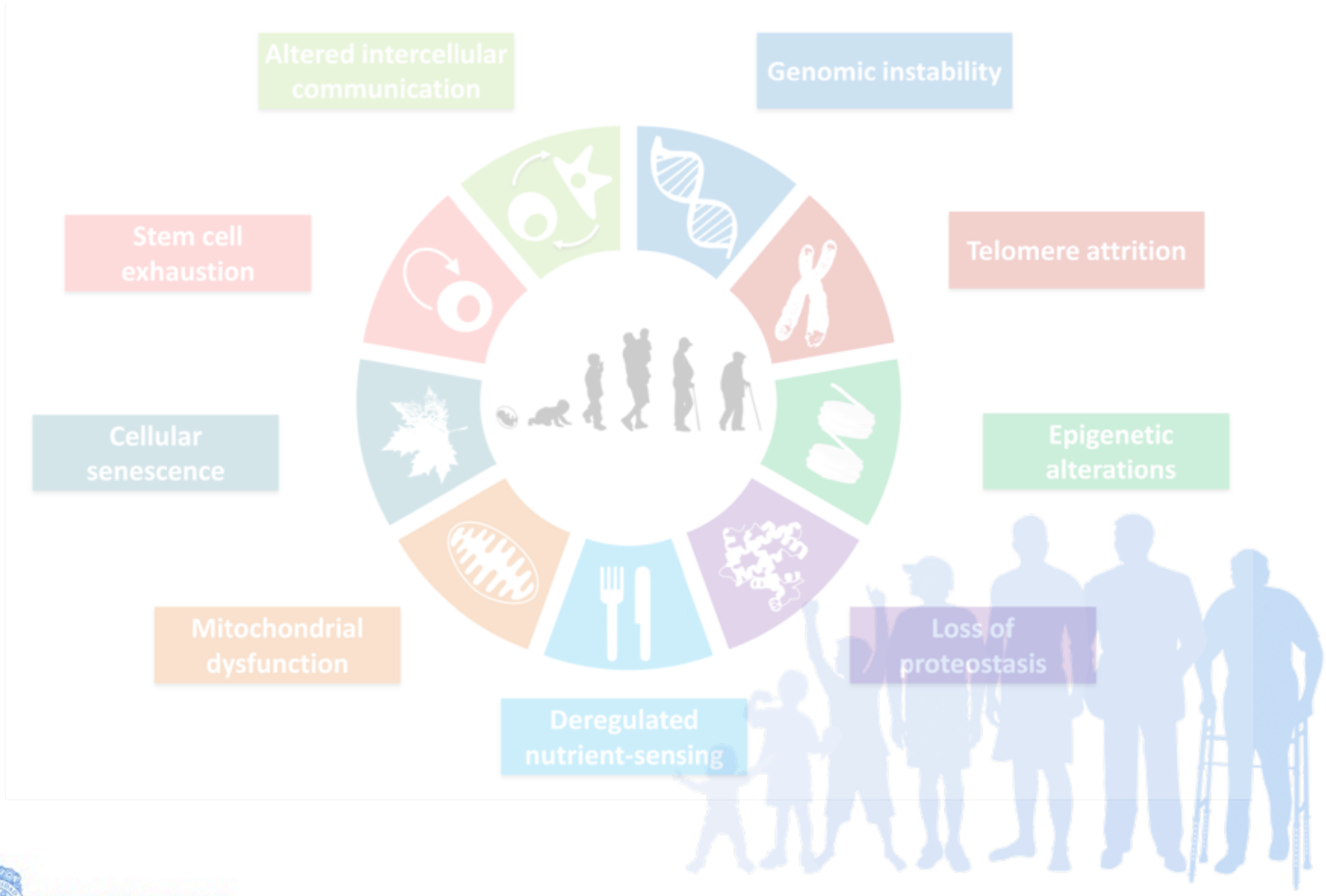
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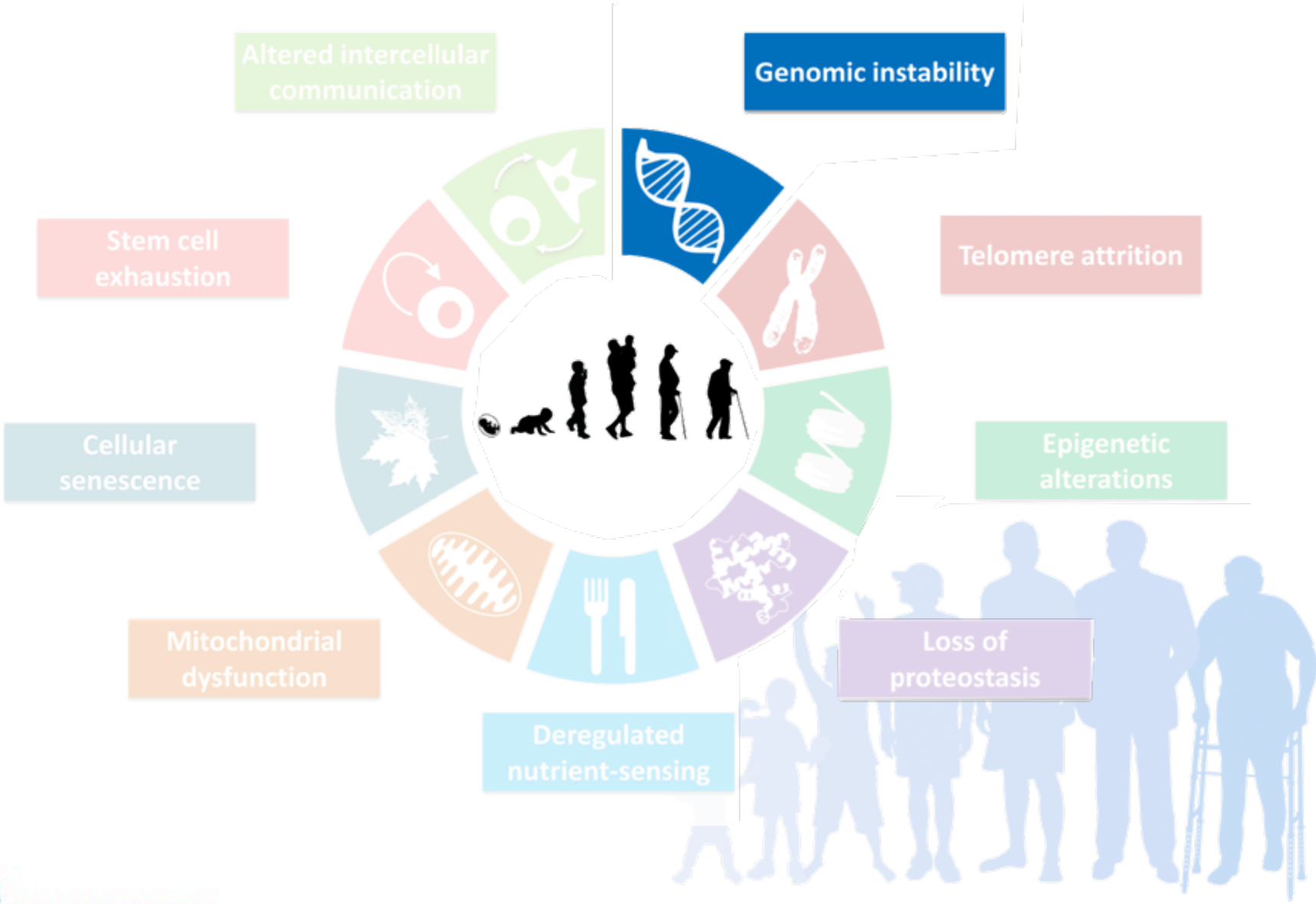
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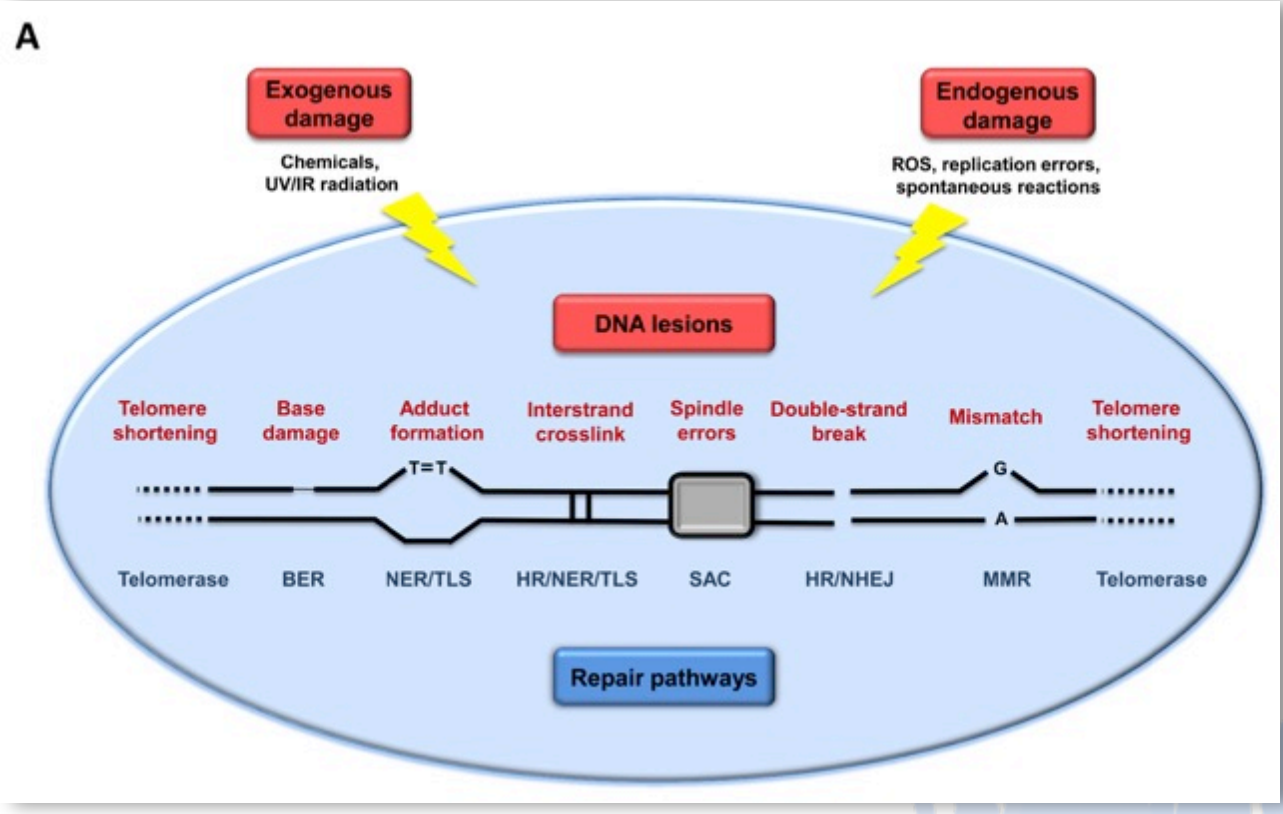
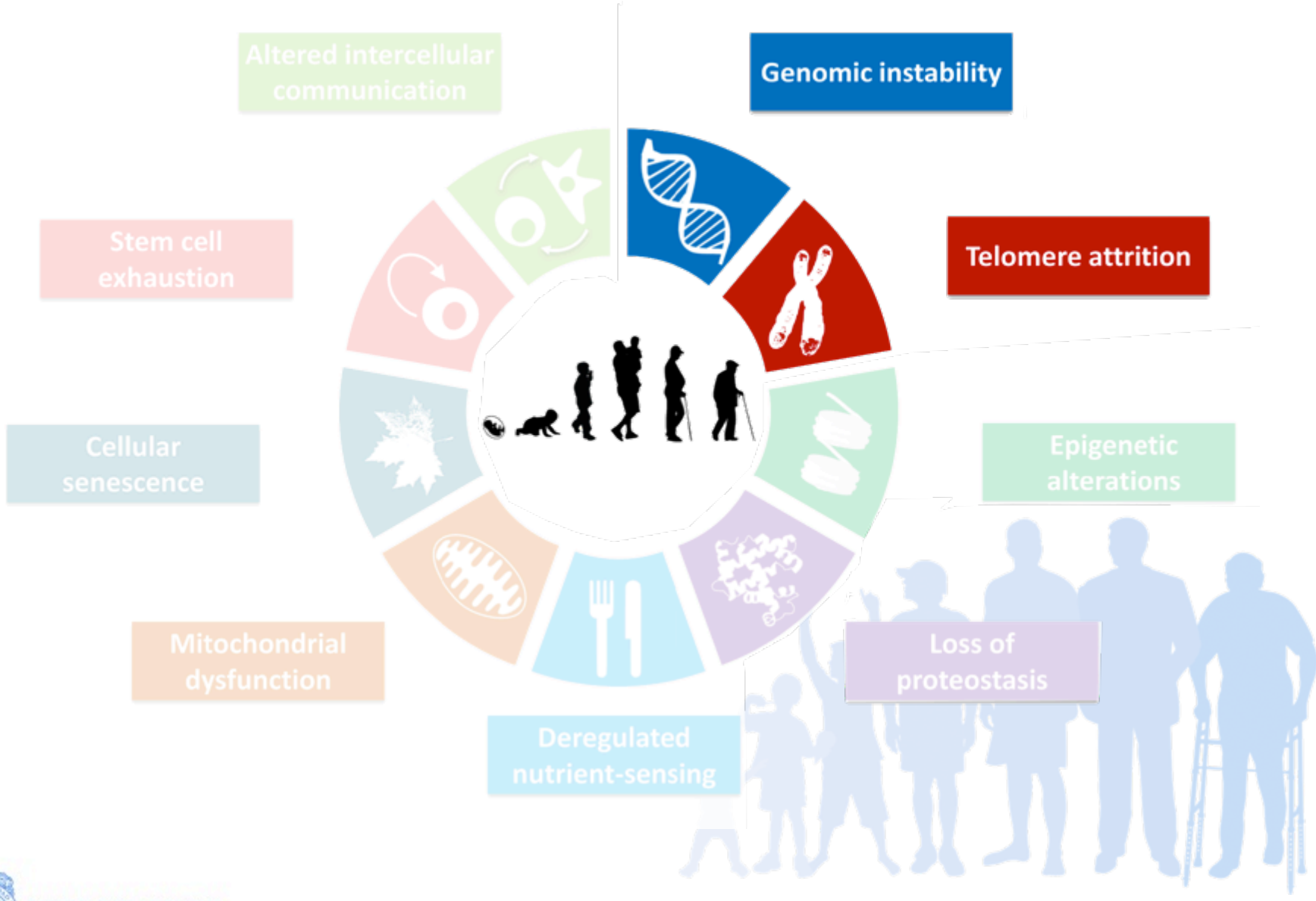


Genomic instability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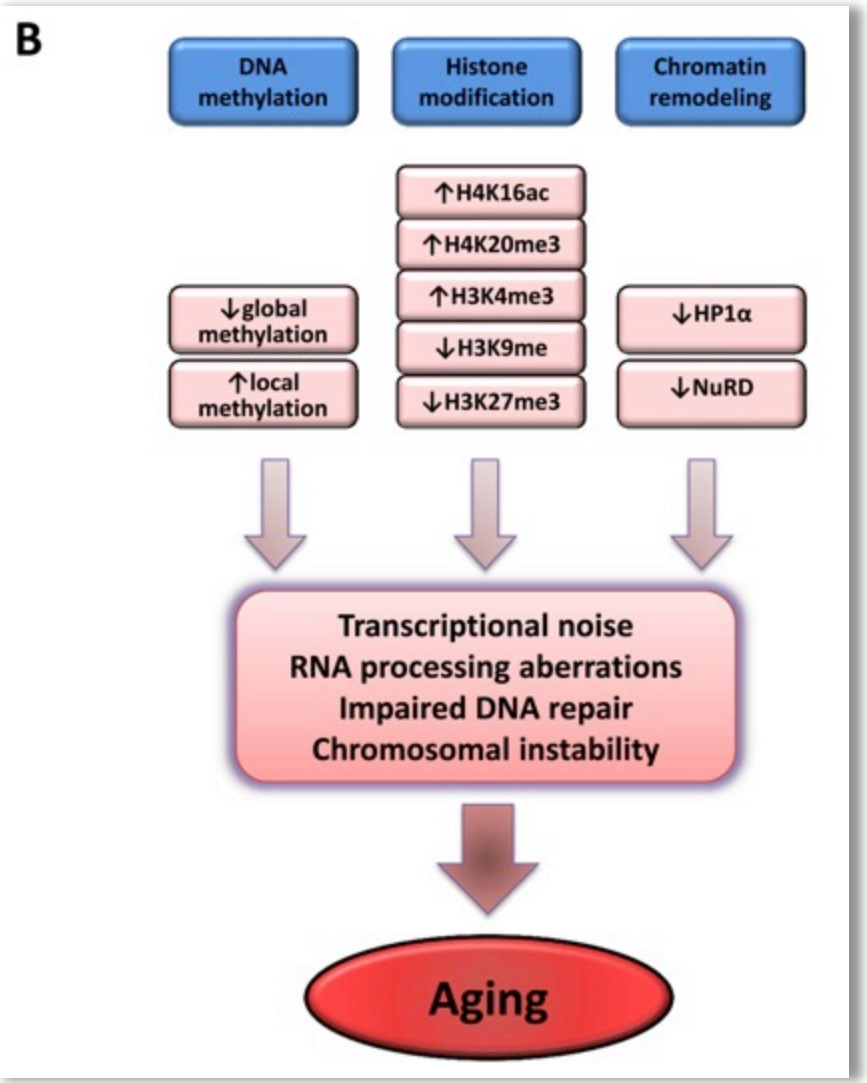
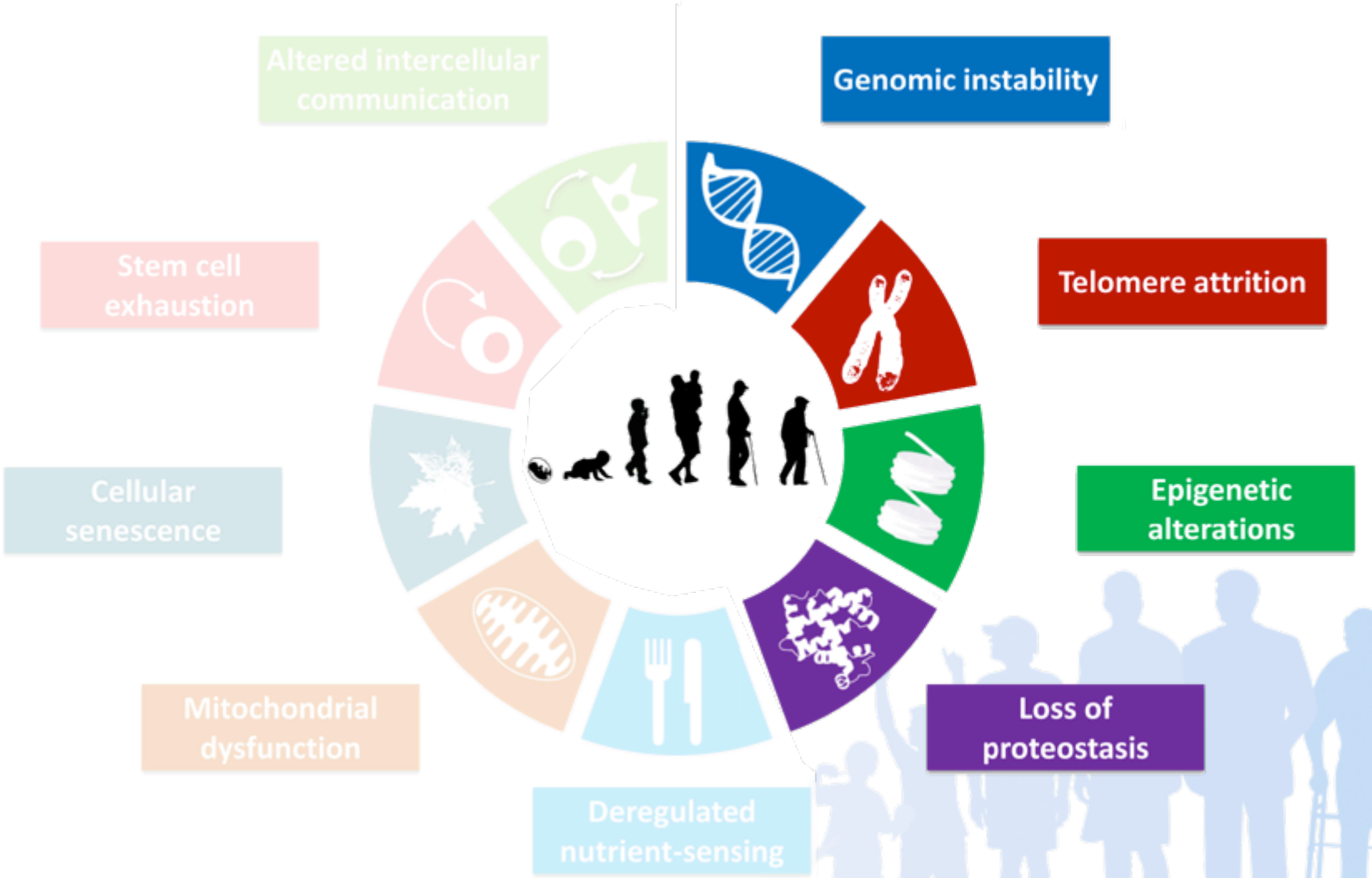


Figure 2. Genomic and Epigenetic Alterations.
A) Genomic instability and chromosome alteration. Endogenous or exogenous agents can stimulate a variety of DNA lesions that are schematically represented on one single chromosome. Such lesions can by repaired by a variety of mechanisms. Excessive DNA damage or insufficient DNA repair favors the aging process. Note that both nuclear DNA and mitochondrial DNA (not represented here) are subjected to age-associated genomic alterations. BER, base excision repair; HR, homologous recombination; NER, nucleotide excision repair; NHEJ, non-homologous end joining; MMR, mismatch repair; ROS, reactive oxygen species; TLS, translesion synthesis; SAC, spindle assembly checkpoint.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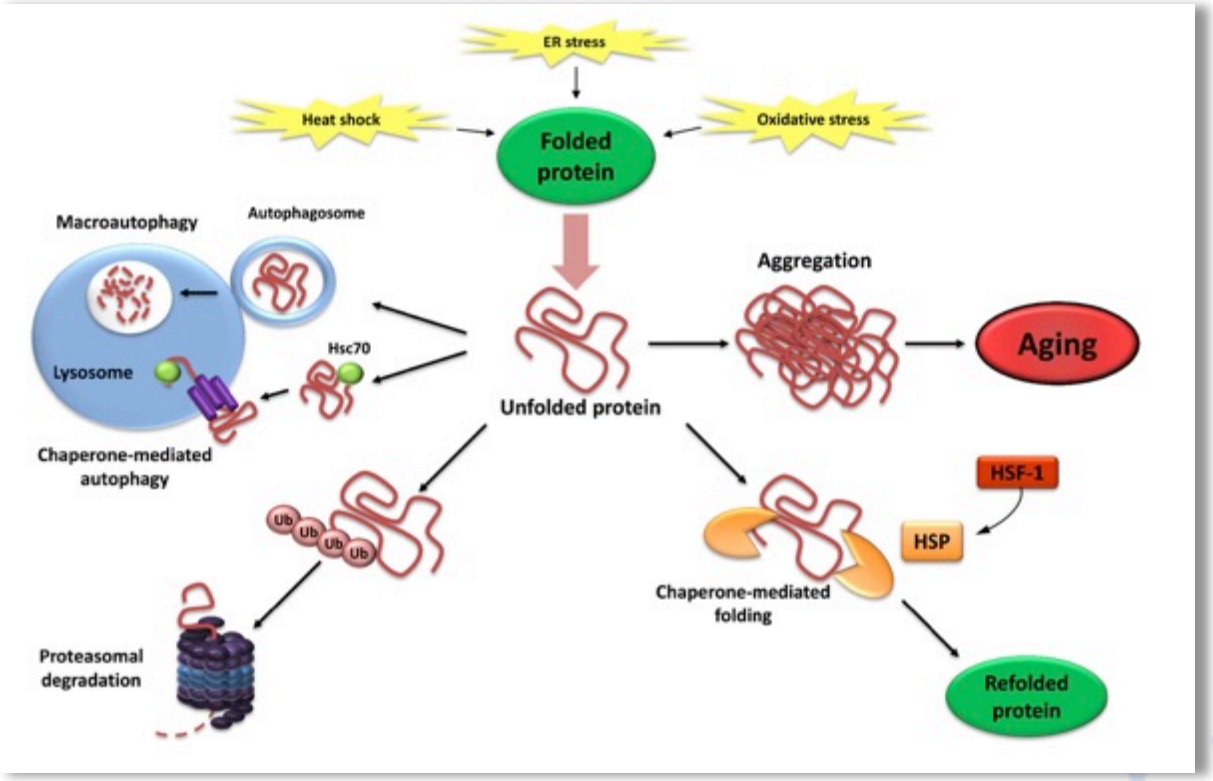

Figure 3. Loss of Proteostasis
Endogenous and exogenous stress causes the unfolding of proteins (or impairs proper folding during protein synthesis). Unfolded proteins are usually refolded by heat-shock proteins (HSP) or targeted to destruction by the ubiquitin-proteasome or lysosomal (autophagic) pathways. The autophagic pathways include recognition of unfolded proteins by the chaperone Hsc70 and their subsequent import into lysosomes (chaperone-mediated autophagy) or sequestration of damaged proteins and organelles in autophagosomes that later fuse with lysosomes (macroautophagy). Failure to refold or degrade unfolded proteins can lead to their accumulation and aggregation, resulting in proteotoxic effects.


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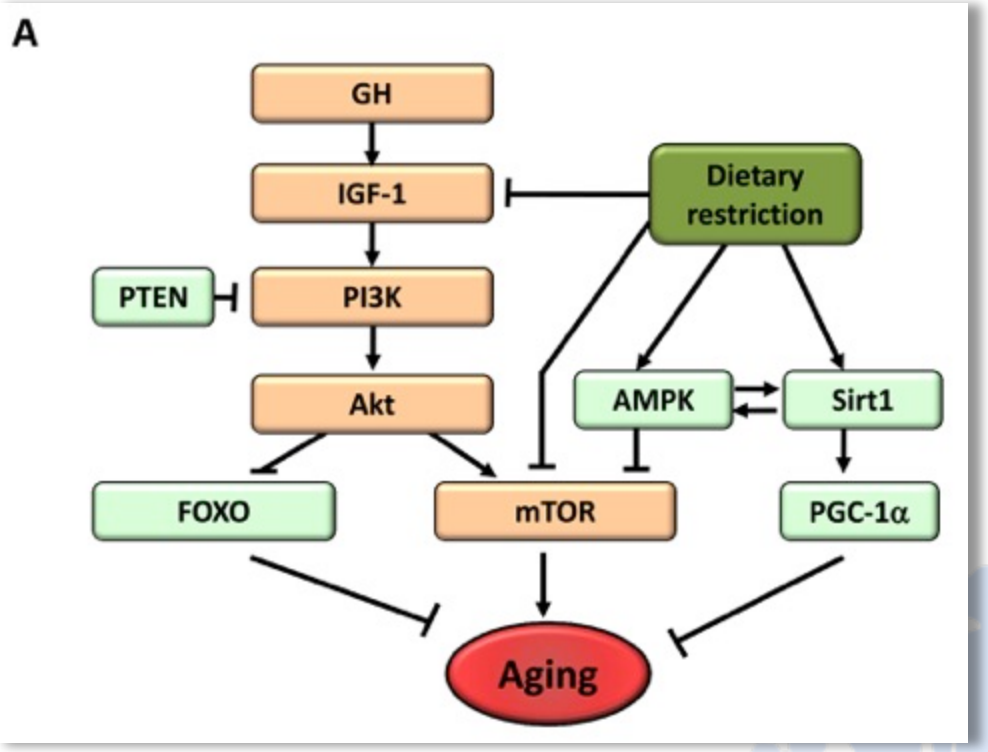

Figure 4. Metabolic Alterations
A) Deregulated nutrient-sensing. Overview of the somatroph axis involving growth hormone (GH) and the insulin/insulin growth factor 1 (IGF-1) signaling pathway, and its relationship to dietary restriction and aging. Molecules that favor aging are shown in orange, while molecules with anti-aging properties are shown in light green.

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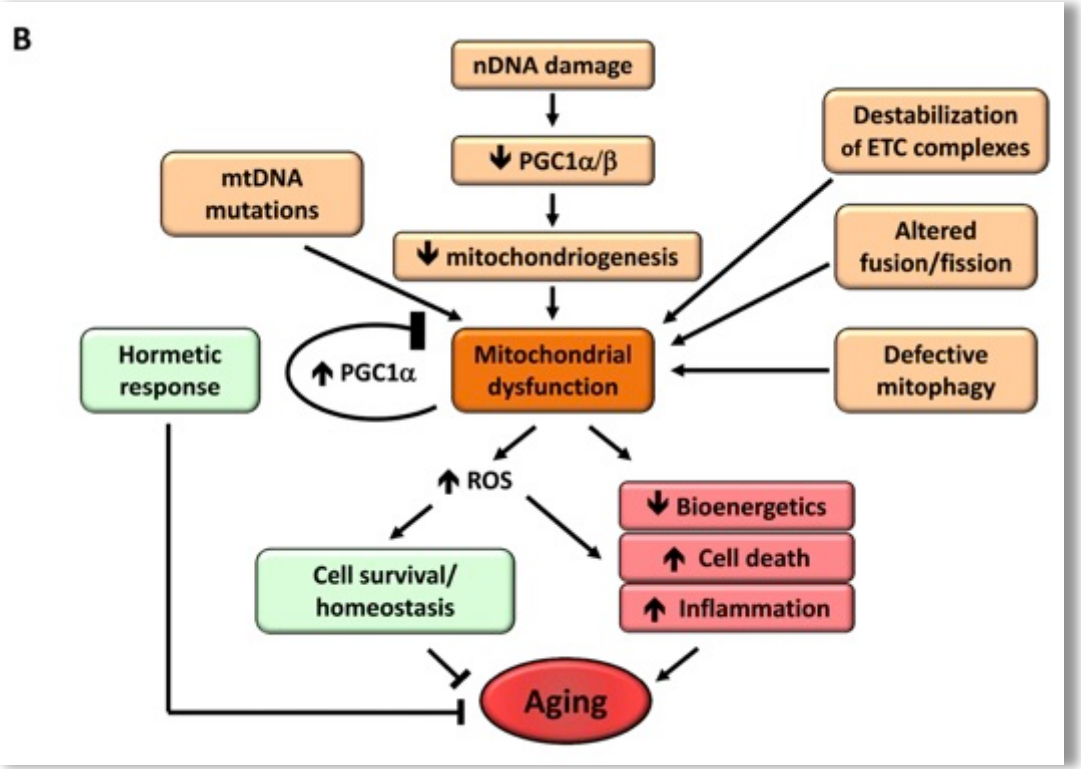

B) Mitochondrial dysfunction. Mitochondrial function becomes perturbed by aging-associated mtDNA mutations, reduced mitochondriogenesis, destabilization of the electron transport chain (ETC) complexes, altered mitochondrial dynamics or defective quality control by mitophagy. Stress signals and defective mitochondrial function generate ROS that, below a certain threshold, induce survival signals to restore cellular homeostasis, but at higher or continued levels can contribute to aging. Similarly, mild mitochondrial damage can induce a hormetic response (mitohormesis) that triggers adaptive compensatory processes.

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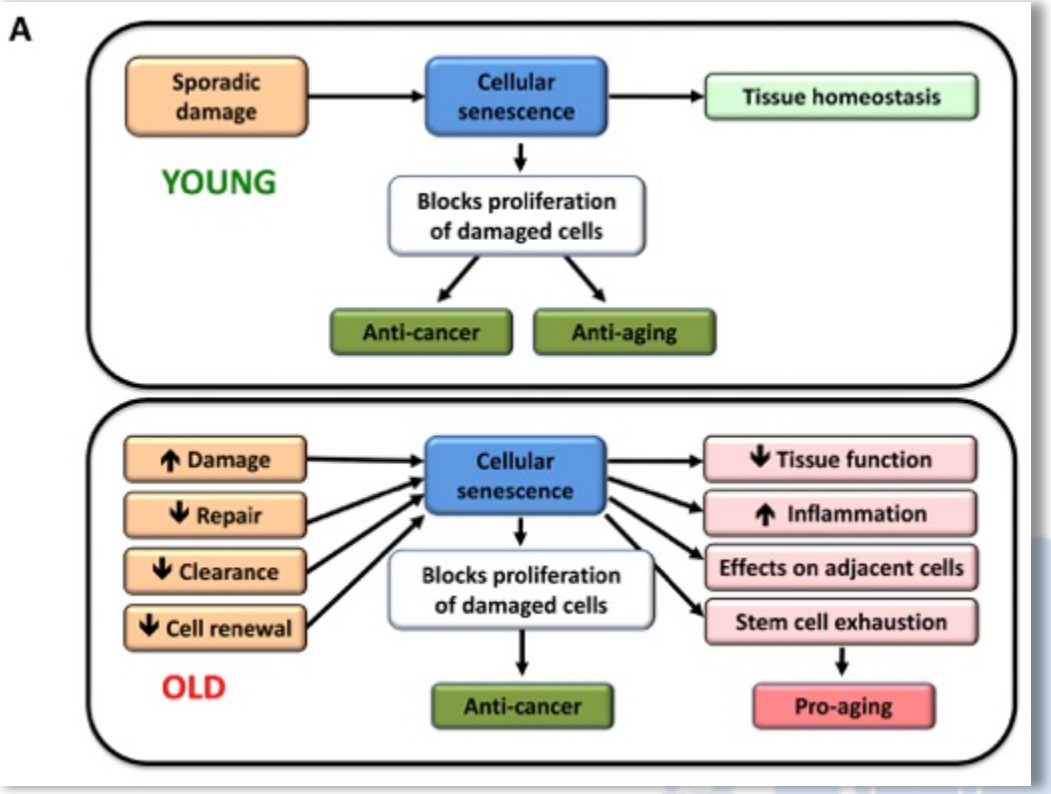
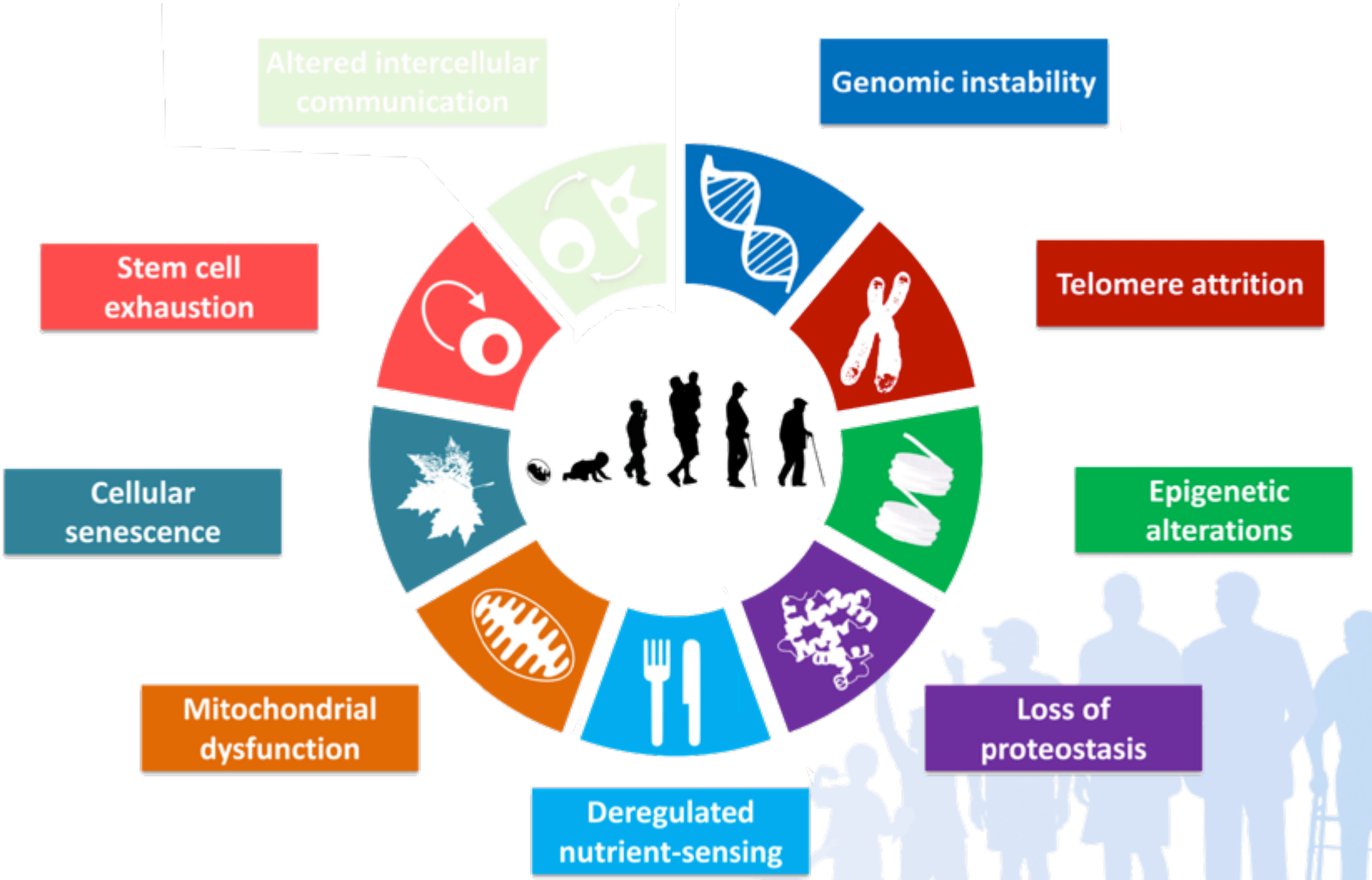


Figure 5. Cellular Senescence, Stem Cell Exhaustion and Altered Intercellular Communication
A) Cellular senescence. In young organisms, cellular senescence prevents the proliferation of damaged cells, thus protecting from cancer and contributing to tissue homeostasis. In old organisms, the pervasive damage and the deficient clearance and replenishment of senescent cells results in their accumulation, and this has a number of deleterious effects on tissue homeostasis that contribute to aging.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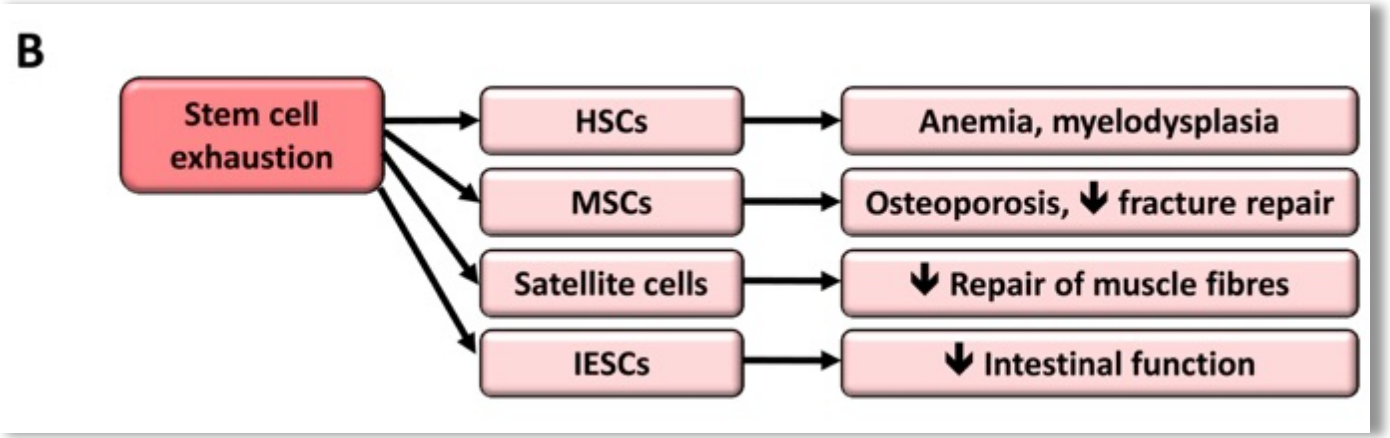
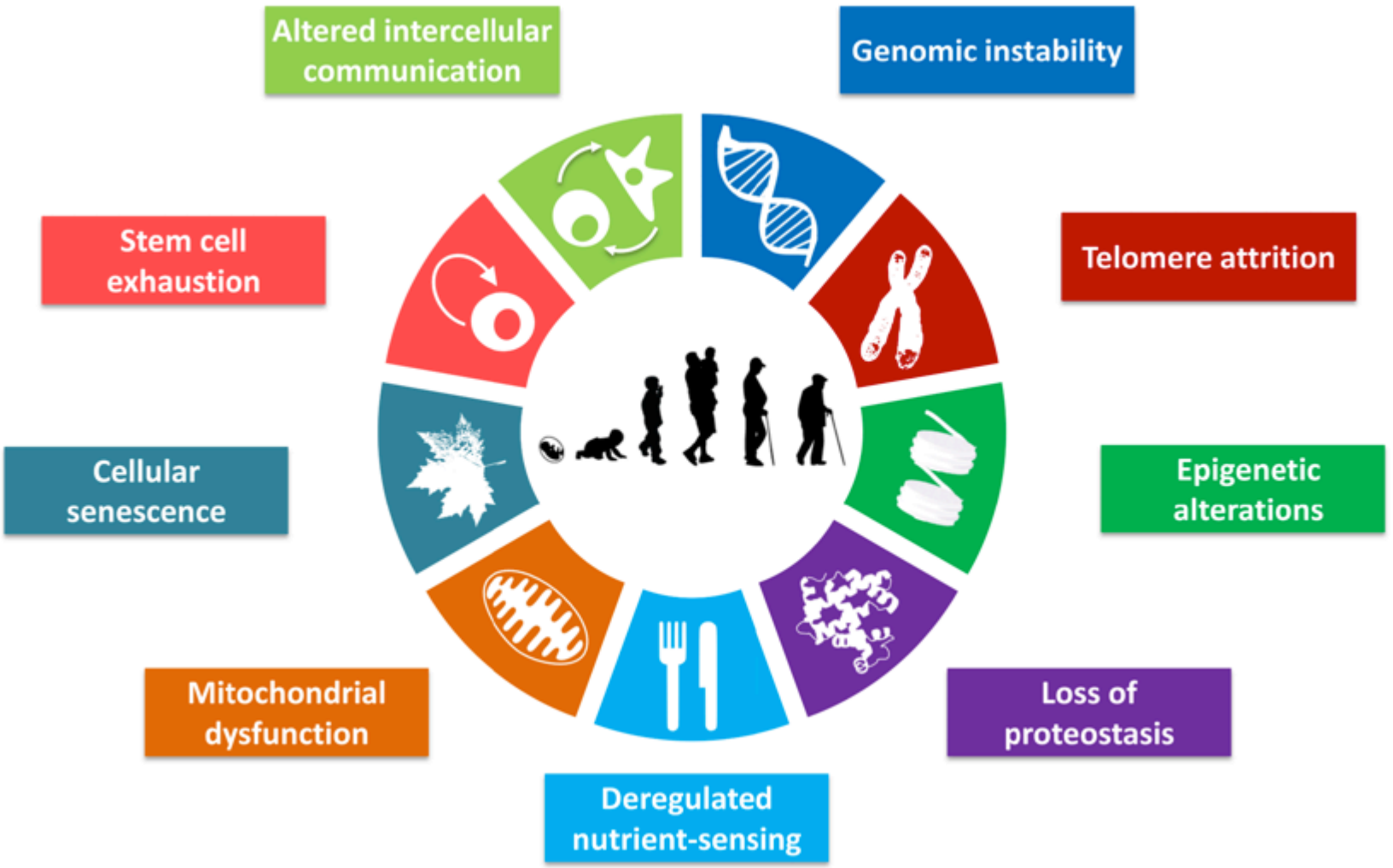


B) Stem cell exhaustion. Consequences of the exhaustion of hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), satellite cells and intestinal epithelial stem cells (IESCs) are exemplified.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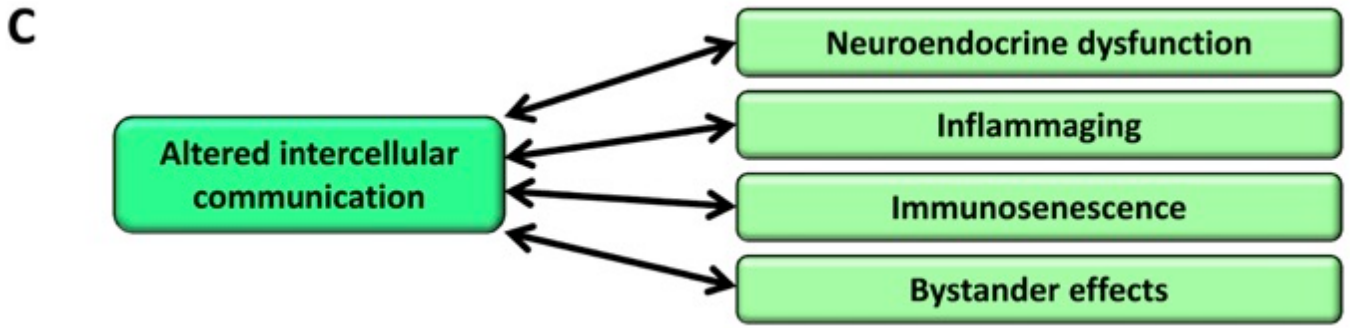
Altered cell communication



C) Altered intercellular communication. Examples of altered intercellular communication associated with aging.

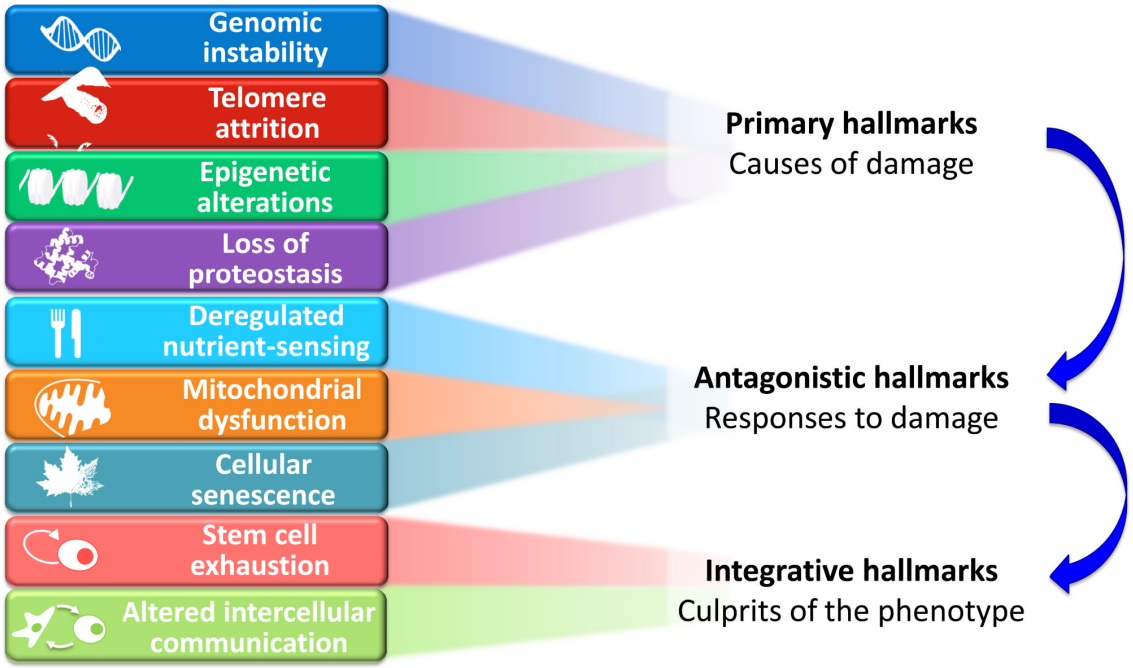


Figure 6. Functional Interconnections between the Hallmarks of Aging
The proposed nine hallmarks of aging are grouped into three categories. In the top, those hallmarks considered to be the primary causes of cellular damage. In the middle, those considered to be part of compensatory or antagonistic responses to the damage. These responses initially mitigate the damage, but eventually, if chronic or exacerbated, they become deleterious themselves. In the bottom, there are integrative hallmarks that are the end result of the previous two groups of hallmarks and are ultimately responsible for the functional decline associated with aging.

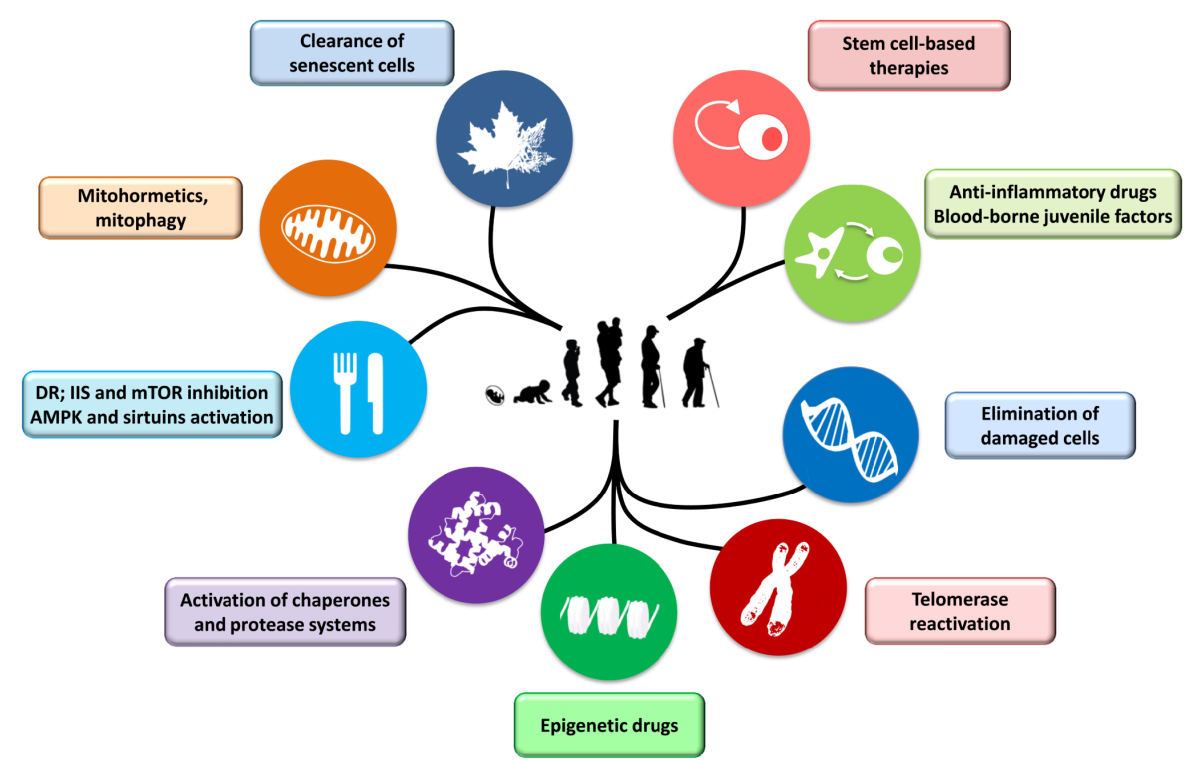


Figure 7. Interventions that Might Extend Human Healthspan
The nine hallmarks of aging are shown together with those therapeutic strategies for which there are proof of principle in mice.

OMNIA FERUNT ULTIMA NECAT

el paso del tiempo

Burnt out or fade away

El "como perder el tiempo"

Agradecimientos

Especialmente a mi mujer (Lali),
a la Facultad de Medicina por hacerme,
a la Sociedad de Geriatría por invitarme
y a Camila Egaña por su paciencia.

¡Y a todos ustedes por escucharme!

FIN