Unravelling the enigma of the complex relationship between aging, senescence, molecular biomarkers and sex/gender influences: a roadmap of open questions

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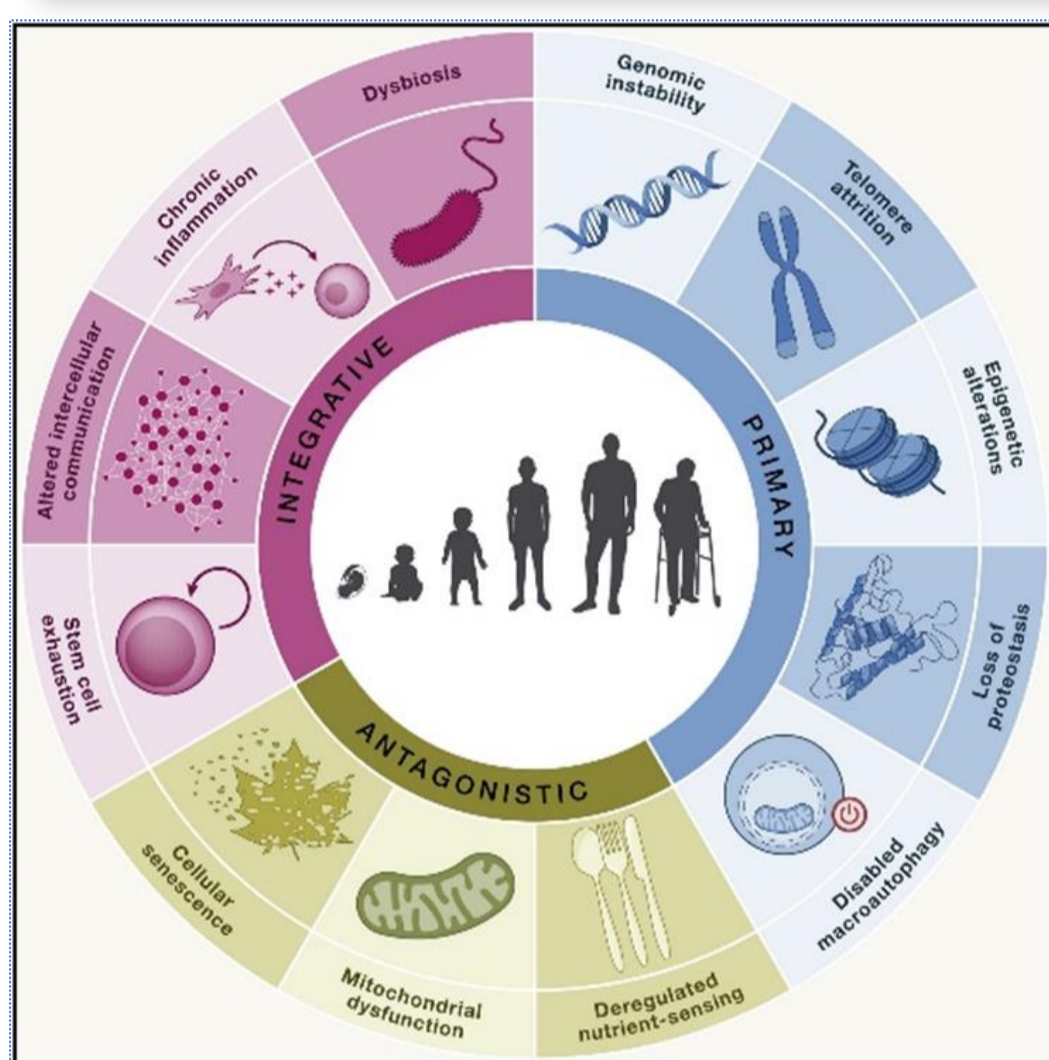## Senescence is a crucial hallmark of aging

Figure 1 [López-Otín C. et al. (2023)]

Aging involves a myriad of molecular changes at the cellular, tissue, and systemic levels. **In 2023**, *Lopez-Otin et al[1]* proposed **12 hallmarks of aging** grouped into three categories: **primary**, **antagonistic,** and **integrative** (**Figure 1**). All the hallmarks are **strongly interconnected** among each other**.**
Senescence, a hallmark of aging, is defined as the **stable arrest of cell cycle associated with a distinctive phenotype.** Cells stop to proliferate but remain viable and apoptosis-resistant and develop a pro-inflammatory **Senescence Associated Secretory Phenotype (SASP)**. Cellular senescence is induced in response to multiple intrinsic and extrinsic *stimuli*, as well as to developmental signals[2]. The accumulation of senescent cells during lifetime is one of the leading causes of aging (**Figure 2**).
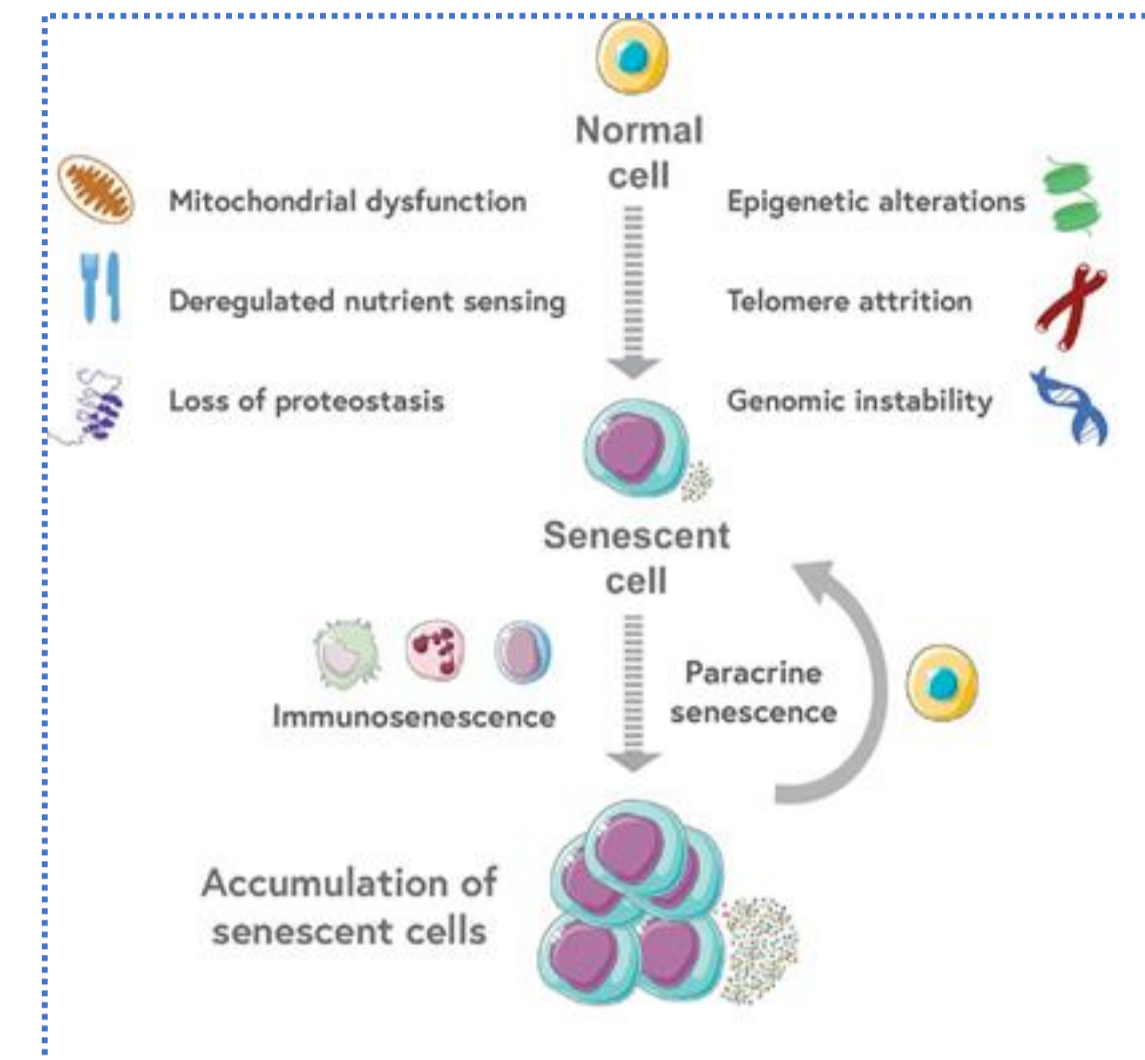

Figure 2 [Borghesan M. et al (2020)]

Are there common and universal molecular signatures of aging and senescence?

Phenotypes of senescent cells are remarkably variable, plastic and heterogeneous. The **most widely used senescence markers** include (*i*) an increased expression of cell cycle inhibitors **p16^{INK4a}** (*CDKN1A*) and **p21^{CIP1}** (*CDKN2A*), (*ii*) an increased activity of the senescence-associated β-galactosidase (**SA-βgal**) enzyme and (*iii*) a decreased expression of the nuclear protein **Lamin B1**. However, **none of these markers** represent an invariable and universal indicator of senescence[3].

To identify reliable molecular biomarkers for tracking the aging process and cellular senescence, the **Aging atlas** and the **Atlas of cellular senescence** have been developed, including data from multiple cell types and tissues exposed to various conditions and analyzed with different experimental approaches[4-6].

GenAge[4]
307 human genes

Aging Atlas[5]
358 human genes

SenNet Cellular Senescence Network[6]
127 human genes

Taking into account the human genes provided by the three atlas, a **molecular signature of 445 human genes** can be considered **relevant for the aging and senescence contributing to numerous signaling pathways** such as: longevity regulating pathway; GnRH signaling pathway; insulin/IGF1/IGF1R signaling axis; PI3K/AKT/mTORC1 network; Ras-MEK-ERK; NF-kappa B, JAK-STAT; P53 signaling; TNF signaling; cytokines signaling; pathway in cancer; response to oxidative stress; lipid and atherosclerosis; DNA damage.

Does sex/gender play a role in aging and age-related diseases ?

Sex refers to the **different biological and physiological properties of male and female cells**, **tissues and organisms**, such as **reproductive organs, chromosomes, hormones and metabolism**. Biological sex is a factor in many conditions including aging, neurodegenerative disease and cancer [7,8]. Data indicate that females sex is more susceptible to DNA damage and senescence onset[8]. **Gender** is a **multifaceted and dynamic concept** that refers to psycho-socio-cultural factors involving self-identity, social interactions, behaviors, expressions, roles and norms, relations, and power. Many **age-related disease** show **sex-specific patterns**[8] and data show a remarkable **gender difference in life expectancy and mortality**[9].
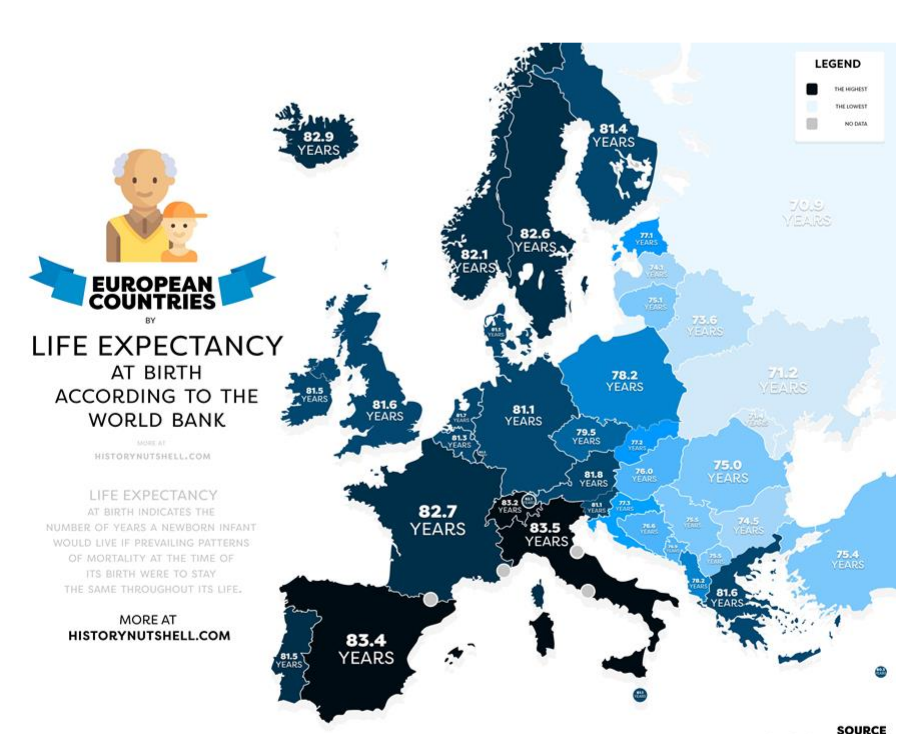

Figure 3

According to **the World bank** the **life expectancy at birth** across central **European countries** ranges from 75- to 83-yrs, with a mean value of 83.5-yrs in Italy (**Figure 3**). **Women have a longer life expectancy than men**, and this disparity may underline the proposed influence of sex on the aging process[7-9]. The primary causes of death in high-income countries include **1. ischemic heart disease 2. stroke 3. chronic obstructive pulmonary diseases 4. Alzheimer's disease (AD) and dementia 5. diabetes mellitus** and **6. cancers**. Notably, all these pathologies show differences in incidence, prevalence, diagnosis, prognosis and treatment between **women** (**Figure 4a**) and **men** (**Figure 4b**).
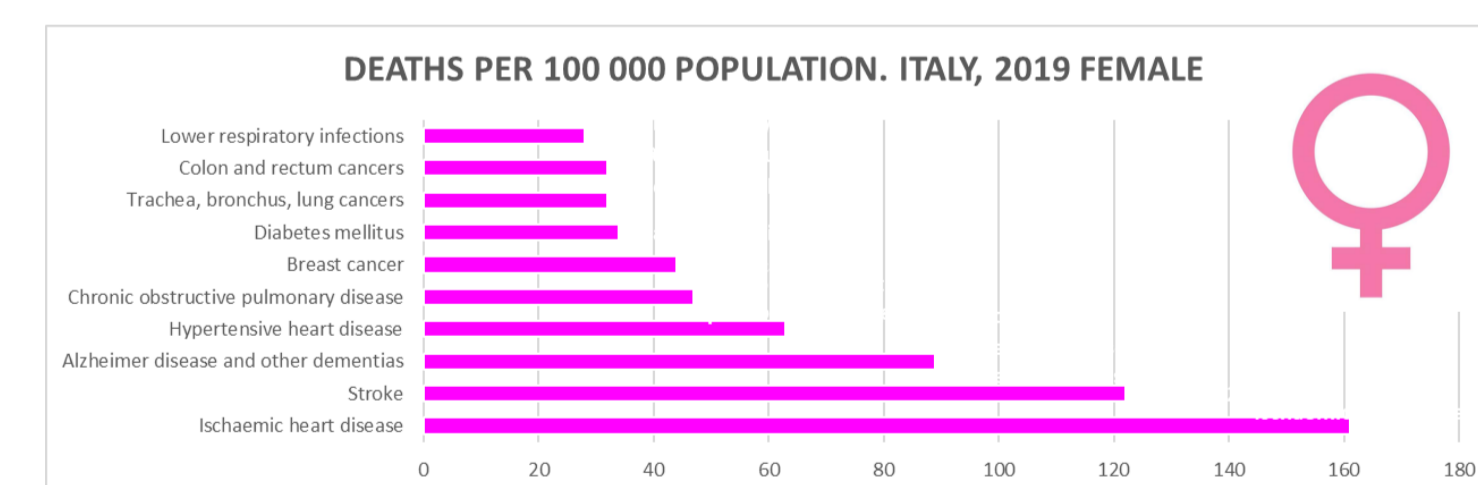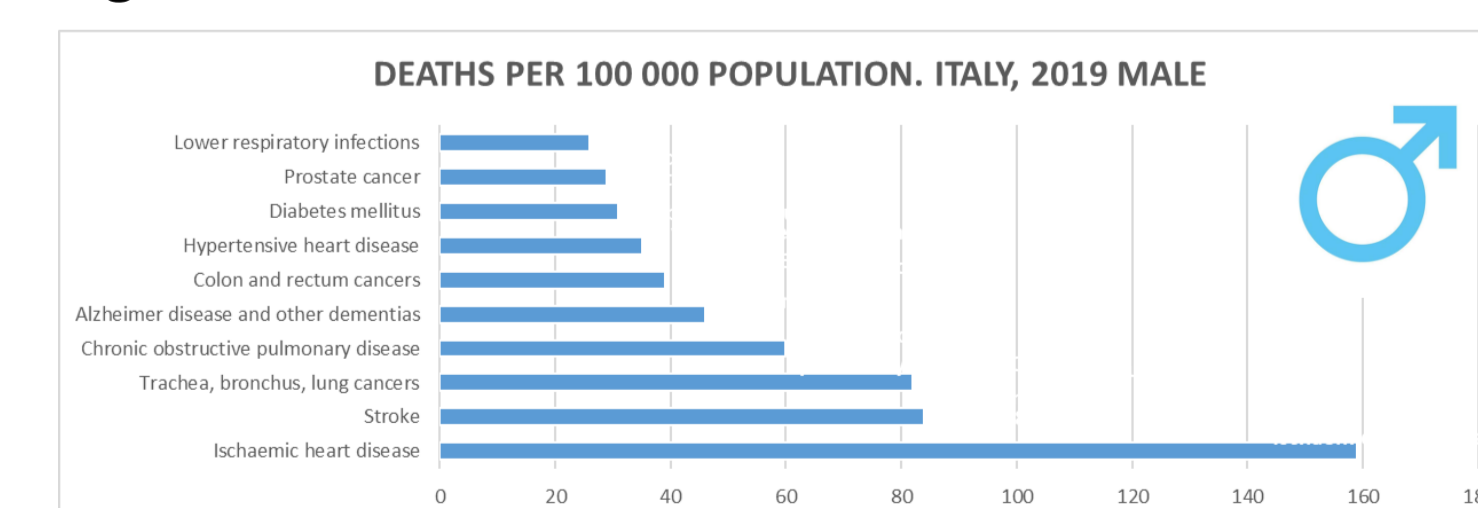

Figure 4a

Figure 4b

An agenda for the future

The influence of biological sex and gender on aging adds a level of intricacy that warrants further investigation.
Advancing in gender-specific medicine is crucial to help the understanding of molecular mechanisms of aging, with the final aim of reducing disparities in prevention, care, and treatment of age-related diseases across all gender.

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