

THE ROLE OF TOXICOLOGY IN AGING RESEARCH: AN INSIGHT

Rahma¹, Agian Jeffilano Barinda^{2,3*}

¹Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

²Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

³Metabolic, Cardiovascular, and Aging Cluster, Indonesia Medical Education and Research Institute (IMERI), Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

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Corresponding Author

Name : Agian Jeffilano Barinda
Email : Agian.jeffilano@ui.ac.id
Mailing address : Departemen Farmakologi Klinik dan Terapeutik, Fakultas Kedokteran Universitas Indonesia, Jl. Salemba Raya No. 6, Jakarta Pusat. 10430, Indonesia
Telephone : +6281355272787
Fax : -
ORCID ID : 0000-0002-5864-3725

Abstract

Aging is defined as a time-dependent decline in organ or tissue function. The rate of physiological aging differs among individuals. In addition to genetics, environmental factors contribute to the acceleration of aging. Gerontogen refers to environmental toxicants that can accelerate cellular aging. Toxicology, which is the study of unintended exposures to toxicants, can provide insight into the aging process. Despite the lack of an excellent biomarker to detect aging at the molecular level, several gerontogens, including UV radiation, have been identified. This study will present concise and brief information regarding several biomarkers that can be used to identify gerontogen, as well as a brief explanation of the fundamental mechanism by which gerontogen causes accelerated aging.

Keywords

Aging, Toxicology, Senescence

Introduction

Aging is one of the primary risk factors for the majority of chronic diseases.¹ Several studies have investigated the relationship between aging and the incidence of chronic diseases such as heart disease,^{2,3} type II diabetes,^{4,5} and cancer.⁶ According to Boersma et al., the prevalence of several chronic diseases in the United States, including arthritis, cancer, chronic obstructive pulmonary disease, coronary heart disease, diabetes, hypertension, and kidney failure, increases with age. Approximately 63.7% of individuals aged 65 and older have more than one of these chronic illnesses.⁷

It is already well-established that specific environmental exposures, such as UV light and cigarette smoke, can cause diseases such as skin and lung cancer. However, it is unknown how these disease-promoting agents relate to aging. Nevertheless, the notion that environmental factors influence aging is not new. Individual variability in gerontogen-environmental factors that can accelerate the cellular aging process-exposure may explain why the rate of physiologic aging varies among individuals. Unlike genetics, toxicology, which analyzes unwanted exposure to toxicants, has not been widely utilized to study the aging process. Meanwhile, many environmental toxins, such as benzene in cigarette smoke or particulate matter in air pollution containing heavy metals such as iron and arsenic, are difficult, if not impossible, to avoid.^{8,9}

This paper will provide insight into the role of toxicology in aging research, including its biomarkers.

Biomarkers for Aging Research

Aging is a time-dependent decline in organ or tissue function. To date, there are at least nine cellular and molecular hallmarks that are thought to play a role in causing and determining aging phenotypes, which include genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, senescence, stem cell exhaustion, and disruption of cellular communications.¹⁰

In general, a few aspects of aging biomarkers need to be considered to identify aging-promoting agents. To begin, it is imperative that a particular marker is applicable across multiple organ systems and is not tissue- or disease-specific. An even more essential and restrictive condition is that the biomarker must play a causal role in aging.⁸

One of the most commonly employed methods to detect aging is by detecting senescence. Senescence is a state of permanent cell-cycle arrest in response to various stressors such as oxidative stress, telomere shortening, DNA damage, and oncogene activation, or as part of physiological processes.^{8,11,12} Senescent cells are

known to accumulate with aging. They are hypothesized to influence aging by altering homeostasis and reducing regeneration capability through the secretion of pro-inflammatory factors.⁸ Due to the close relationship between aging and senescence, senescence biomarkers can be used to identify aging. However, to date, there is no universal marker for senescence detection. Therefore, the recommended approach for detecting senescence is to use two or more biomarkers representing different processes that occur in senescent cells, including markers for cell-cycle arrest, structural changes, apoptosis resistance, and senescence-associated secretory phenotype.¹³⁻¹⁵ A detailed explanation of these biomarkers has been described in recent publication.¹³

Gerontogen

In addition to genetic factors, environmental factors play a role in accelerating the aging process. Environmental factors that can accelerate the aging process on a molecular level are termed gerontogens. Gerontogens include environmental substances (such as arsenic, benzenes, etc.) to which humans are often unwittingly exposed. These may also include non-chemical exposures like ionizing radiation or ultraviolet light. Not only that, but gerontogens also include intentional exposures, whether for pleasure (e.g., cigarette smoke) or as unexpected side effects of therapeutic therapy.⁸

Most research on the toxicology of aging has focused on DNA-damaging agents and the activation of DNA-damage response (DDR). For example, UV exposure can accelerate aging by causing DNA damage. UVA and UVB can indirectly damage DNA by producing reactive oxygen species (ROS). UVB can directly damage DNA by forming cyclobutene pyrimidine dimer (CPD).¹⁶ DNA damage will activate the DDR leading to the cell-cycle arrest.¹⁷

While DNA damage and DDR activation can both contribute to senescence, this does not necessarily imply that senescence always occurs in conjunction with DNA damage and DDR activation. In fact, DDR activation itself can occur in the absence of DNA damage. Previous research indicate that non-DNA-damaging agents can also cause increased expression of the cyclin-dependent kinase inhibitor p21 and evoke cellular senescence without causing detectable DNA damage as measured by the comet assay. Nevertheless, proteins that constitute DDR are still present in these cells.¹⁸

Senescence can also occur in the absence of both DNA damage and DDR activation, as in oncogene activation or tumor-suppressor gene suppression. There appear to be other pathways that do not involve DNA damage, such as senescence in human mammary epithelial cells that is related to TGF- upregulation rather than

DDR pathway, upon induction by oncogenic Ras overexpression. Numerous interrelated studies are currently presented in a review article devoted to this topic.¹⁸

Hence, forthcoming investigations into gerontogens might encompass not only DNA-damaging agents, but also other prevalent toxicants that can potentially trigger senescence and hasten the aging process via alternative mechanisms.¹⁸

Conclusion

Several studies have shown that various environmental toxicants can accelerate the aging process by promoting senescence. Unfortunately, we are constantly subjected to a wide range of these gerontogens on a daily basis. Many additional agents may have not yet been identified but have the potential to accelerate aging and promote subsequent aging-related diseases. This highlights the significance of bringing toxicology into aging research. Future research may focus on discovering universal biomarkers to facilitate gerontogen identification.

Conflict of Interests

The authors have no conflicts of interest to declare.

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References

1. Tchkonja T, Kirkland JL. Aging, Cell Senescence, and Chronic Disease. *JAMA*. 2018; 320: 1319.
2. Tyrrell DJ, Goldstein DR. Ageing and atherosclerosis: vascular intrinsic and extrinsic factors and potential role of IL-6. *Nat Rev Cardiol*. 2021; 18: 58–68.
3. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. *Circ Res*. 2012; 110: 1097–108.
4. Palmer AK, Tchkonja T, LeBrasseur NK, et al. Cellular senescence in type 2 diabetes: A therapeutic opportunity. *Diabetes*. 2015; 64: 2289–98.
5. Fazeli PK, Lee H, Steinhilber ML. Aging Is a Powerful Risk Factor for Type 2 Diabetes Mellitus Independent of Body Mass Index. *Gerontology*. 2020; 66: 209–10.
6. The importance of aging in cancer research. *Nat Aging*. 2022; 2: 365–6.
7. Boersma P, Black LI, Ward BW. Prevalence of multiple chronic conditions among US adults, 2018. *Prev Chronic Dis*. 2020; 17: 1–5.
8. Sorrentino JA, Sanoff HK, Sharpless NE. Defining the toxicology of aging. *Trends Mol Med*. 2014; 20: 375–84.

9. Vellee ST, Wise JP. Among Gerontogens, Heavy Metals Are a Class of Their Own: A Review of the Evidence for Cellular Senescence. *Brain Sci*; 13. Epub ahead of print. 2023.
10. López-Otín C, Blasco MA, Partridge L, et al. The hallmarks of aging. *Cell*. 2013; 153: 1194.
11. Gorgoulis V, Adams PD, Alimonti A, et al. Cellular Senescence: Defining a Path Forward. *Cell*. 2019; 179: 813–27.
12. Gasek NS, Kuchel GA, Kirkland JL, et al. Strategies for targeting senescent cells in human disease. *Nat Aging*. 2021; 1: 870–9.
13. González-Gualda E, Baker AG, Fruk L, et al. A guide to assessing cellular senescence in vitro and in vivo. *FEBS Journal*. 2021; 288: 56–80.
14. Tuttle CSL, Luesken SWM, Waaijer MEC, et al. Senescence in tissue samples of humans with age-related diseases: A systematic review. *Ageing Res Rev*. 2021; 68: 101334.
15. Kohli J, Wang B, Brandenburg SM, et al. Algorithmic assessment of cellular senescence in experimental and clinical specimens. Springer US. 2021.
16. Fitsiou E, Pulido T, Campisi J, et al. Cellular Senescence and the Senescence-Associated Secretory Phenotype as Drivers of Skin Photoaging. *J Invest Dermatol*. 2021; 141: 1119–26.
17. Di Micco R, Krizhanovsky V, Baker D, et al. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol*. 2021; 22: 75–95.
18. Bielak-Zmijewska A, Mosieniak G, Sikora E. Is DNA damage indispensable for stress-induced senescence. *Mech Ageing Dev*. 2018; 170: 13–21.