In a recent review article published in Cell, L´opez-Otín and colleagues conducted an exhaustive literature review and described 12 hallmarks of aging. The updated model of aging comprehensively captures the key characteristics of the aging phenotype and incorporates new pathways that play a crucial role in age-related processes. Although the updated hallmarks of aging provide a useful framework for describing the phenotype of aging, aging itself is a result of mechanistically complex and interrelated processes that happen during the lifespan of the organism. Here, I propose to shift the focus from a systematic description and categorization of the hallmarks of aging to a model that separates the early, molecular origins of changes from cellular and tissue responses and represents the sequential and causative character of changes in aging. The proposed model aims to prompt discussion among the aging research community, guide future efforts in the field, and provide new ideas for investigation.

In the past decade, significant progress has been made in the field of aging, with numerous preclinical and clinical investigations on aging and age-related diseases. In a recent review article published in Cell, L´opez-Otín and colleagues provided an updated view of the hallmarks of aging. The authors conducted an exhaustive literature review and described 12 hallmarks of aging, grouped into three categories: primary, antagonistic, and integrative. This updated model of aging comprehensively captures the key characteristics of the aging phenotype and incorporates new pathways that play a crucial role in age-related processes, such as dysbiosis, chronic inflammation, and disabled macroautophagy. The authors also made tremendous efforts to integrate the updated hallmarks of aging with each other, as well as with the recently proposed hallmarks of health, and provided several examples of mechanistic interpretation of the model. This comprehensive overview of the hallmarks of aging will undoubtedly serve as a reference and a starting point for future investigations.

Although the updated hallmarks of aging provide a useful framework for describing the phenotype of the process, aging is a result of mechanistically complex and interrelated changes that happen constantly during the lifespan of the living organism. When the nine hallmarks of aging were first introduced in 2013, little was known about the mechanisms of aging. Since then, many research groups have described various mechanisms underlying this process, introducing the concept of the sequential character of changes in time and the molecular basis of the process. Therefore, I believe that the hallmarks of aging will benefit from the inclusion of information of temporal and sequential character of the process of aging. The aim of this commentary is to discuss the key mechanisms underlying the aging phenotypes and how these are linked to each aging hallmark and to each other. In doing so, I propose to shift the focus from a systematic description and categorization of the hallmarks of aging to a model of aging that attempts to dissect the timing and causes of affected phenotypes.
to repeated stress throughout the life of the organism accumulate over time and eventually become detectable in aged individuals as “hallmarks” of aging. As the early events of aging occur in the early stages of the process, they are attractive targets for developing interventions to slow the upstream processes of aging and delay the onset of age-related diseases.

Intermediate events of aging include cellular responses to stress-induced molecular alterations and are engaged in adjusting cellular processes to the newly established but changing molecular makeup of the cell. These physiological reactions aim to maintain cellular homeostasis and help cells re-establish a healthy equilibrium. Intermediate events of aging include inflammation, proteostasis, autophagy, energy homeostasis, senescence, establishing energy homeostasis, and rewiring of cellular metabolism. If not resolved, molecular and cellular alterations due to repeated stress throughout the life of the individual trigger late events of aging, which manifest as aging phenotypes. Late events of aging result in progressive deterioration of organ function and include stem cell exhaustion, organ dysfunction, loss of tissue integrity, immune system dysfunction, for example, chronic low levels of inflammation, and alterations in tissue–tissue interactions and cell–cell communication. Molecular, cellular, and phenotypic processes of aging are interconnected, and progression in one process induces the progression of all other processes.

At present, investigational therapeutic approaches targeting aging phenotypes are geared mostly toward reverting aging symptoms rather than targeting the underlying molecular and cellular mechanisms. However, recognizing the aging phenotype is crucial for deciphering the mechanisms underlying aging and age-related diseases.

The proposed model of aging is influenced by a recent review by Campello and colleagues discussing the molecular and metabolic mechanisms of retinal aging. The model is also inspired by peer discussions regarding the mechanisms of aging, the molecular and physiological changes occurring during the lifespan, and the phenotypic changes that are recognized as “aging” by experts and nonexperts alike. The model presented here is not final; instead, it should serve as a reference for new ideas and a starting point for a deeper understanding of aging at the cellular and molecular levels. I hope that this model will help researchers studying aging to design future mechanistic studies and develop reliable animal models of aging, which are currently limited.

We cannot fully delineate complex biological processes such as aging without addressing the molecular and cellular mechanisms that contribute to the different characteristics of aging and without dissecting the temporal and causal sequence of events. In an effort to provide a more holistic view of aging, I have presented an integrative model for the hallmarks of aging and proposed a novel way of presenting the current knowledge of aging-related processes. Despite recent progress in the field, there is still much to learn about the mechanisms of aging. Rather than establishing a status quo, the proposed model aims to prompt discussion among the aging research community, guide future efforts in the field, and provide new ideas for investigation. This “three-wheeled gears” model can also help identify new measures of...
aging and establish new endpoints for clinical trials aimed at reversing or slowing aging. As argued here, a better understanding of the mechanisms of aging is crucial for the development of effective interventions that target molecular pathways and early cellular events that drive aging rather than solely reversing one or more of the phenotypes of aging.

Acknowledgments

The author wishes to thank the members of the DSK laboratory for the discussions, Beth Schachter for critical reading of the early version of this article, Christos Evangelou for professional editing, many colleagues for discussions during recent meetings, and the editors of Aging Biology for helpful comments.

Conflicts of Interest

The authors declare that no conflicts of interest exist.

Accepted March 7, 2023
Published July 28, 2023

References