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Hallmarks of Aging: Causes and Consequences

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Abstract

In a recent review article published in Cell, López-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*, López-Otín and colleagues[1] 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 an important 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[2], 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[3], little was known about the mechanisms

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Conflicts of Interest

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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.

The aging process is commonly divided into early and late events, with a clear distinction between aging phenotypes and the underlying molecular events. Aging encompasses molecular, physiological, and phenotypic changes with different clinical relevance and different short-term or long-term outcomes if targeted using pharmacological interventions. Therefore, I propose a “three-wheeled gears” model (Fig. 1) to describe the early (upstream), intermediate, and late (downstream) events of aging, which roughly correspond to the primary, antagonistic, and integrative hallmarks of aging proposed by López-Otín and colleagues[1]. All gears of the model are interconnected, and a wheel movement representing progress or accumulation induces movement of all other wheels. In this model, I suggest cellular stress could be one of the starting points of the aging process, acknowledging that the type of stressor can differ for each cell, tissue, and organ.

Environmental cues (e.g., pollution, infection, heat, and cold) cause cellular stress and disturbances in fundamental molecular processes that can induce epigenetic changes, transcriptional noise, release of chromatin to the cytoplasm, nuclear and mitochondrial DNA damage, loss of translational integrity, oxidative stress, and breakdown of the cell membrane. The last process, despite the long-existing theory[4,5], and supported by increasing amount of data[4,6], is relatively less studied when compared to other processes in the group.

The type of cellular stress influences which molecular processes are primarily affected in the cell; however, several processes can be affected by the same stressor. The early events of aging are highly interconnected and impact each other, often inducing several responses (see below). These early molecular events are challenging to detect without specialized technologies and tests, which are rarely available in the clinic. Molecular alterations and disturbances in cellular processes due to cellular stress create “inflection points” that need to be resolved to allow the cell to revert to a healthy state. If not resolved, molecular changes due 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, and rewiring of cellular metabolism, including lipids, sugars, and proteins sensing and turnover. Although these are natural processes of the cell, their prolonged deregulation changes the status of the cell and can finally manifest as *antagonistic hallmarks of aging*. Intermediate events of aging are promising therapeutic targets, as interfering with these pathways can help prevent the progression of cellular changes and slow the deterioration of cellular health.

Late events of aging involve the phenotypic manifestation of the changes that have occurred at the molecular and physiological levels and are closely related to the *integrative* hallmarks of aging described by López-Otín and colleagues[1]. Although aging phenotypes may differ depending on the tissue, they all result in progressive deterioration of organ function. Late events of aging include stem cell exhaustion, immune system dysfunction, including chronic inflammation, organ dysfunction, loss of tissue integrity, and alterations in tissue–tissue interactions and cell–cell communication, including dysbiosis. These processes are interconnected and can influence one another as well.

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[7] 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.

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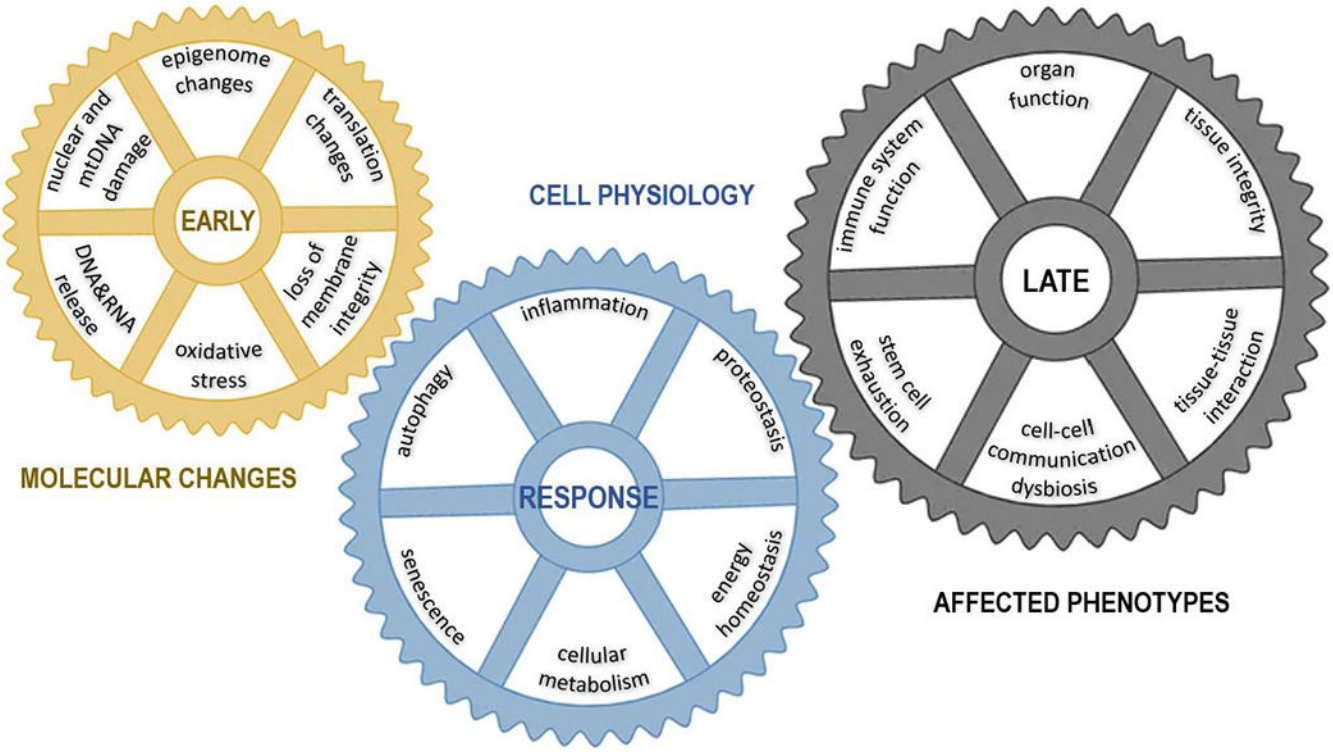

Figure 1. Mechanistic view of the hallmarks of aging.

Schematic overview of the molecular, cellular, and phenotypic processes of aging, grouped into early, intermediate, and late events, emphasizing the sequential and temporal character of the process of aging. Any type of stress/disturbance can induce epigenetic changes, transcriptional noise, nuclear and mitochondrial DNA damage, loss of cell membrane integrity, and oxidative stress, among other molecular disturbances. Intermediate events of aging encompass cellular responses to stress-induced molecular alterations and include activation of inflammation, proteostasis, autophagy, 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.