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EDITORIAL

Loss of molecular resilience as the ultimate outcome of aging biology

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Hallmarks and pillars

The image of The Hallmarks of Aging (Fig. 1 in Lopez-Otín et al. [1]) is almost an obligatory slide to be shown at the beginning of most scientific presentations dealing with aging biology or geroscience. The hallmarks have been used extensively as a way of reaffirming that the talk about to be given is not on a bizarre obscure subject, but rather, it fits within the mainstream of the field, and thus, the audience would do good by listening carefully.

But what is the use of the hallmarks, other than reassurance that your area of research is within the mainstream? After all, the selection of which processes belong or not within the hallmarks and pillars was somewhat arbitrary, and indeed, the list was expanded in an update published by the same authors 10 years later [2]. In fact, while we tend to think of them as individual entities and pathways, the reality is that all the hallmarks are tightly interconnected in a systems biology network, so that affecting one hallmark will also result in changes in all others, thus thwarting attempts to identify which of the hallmarks might act as a leading driver, or rheostat that drives the ability to adapt to challenges and continuing to function. In fact, it is likely that the trigger/rheostat might be different in each individual, depending on specific gene and environment characteristics, but it is nevertheless precisely this "systems biology" nature, including multiple interacting pathways and processes, that makes defining and studying aging so complex: the deterioration of health with aging is actually the result of a constellation of multiple small decrements in function over time, affecting multiple systems [3]. Indeed, the opposite (a major catastrophic failure in a specific system) is called either disease, or death, but not aging. As a corollary, it appears that since overall health can only be achieved by the homeostatic coordination of all our physiological systems, all the processes described as hallmarks of aging can in fact be described as hallmarks of life since the complete collapse of any one of these processes appears to be incompatible with life and lead to a complete failure to thrive, ultimately resulting in death (L. Ferrucci, pers. comm.). In contrast, a small decline in any of these functions is still likely to be compatible with life as long as the organism is able to compensate, perhaps by attaining a new homeostatic equilibrium. Extending that argument, we might need to keep updating the "hallmarks of aging" every 10 years or so, and keep adding more and more hallmarks, until ultimately, we might realize that every one of our physiological systems plays a role in maintaining our health and weakening of any and all of them will lead to deteriorating health without

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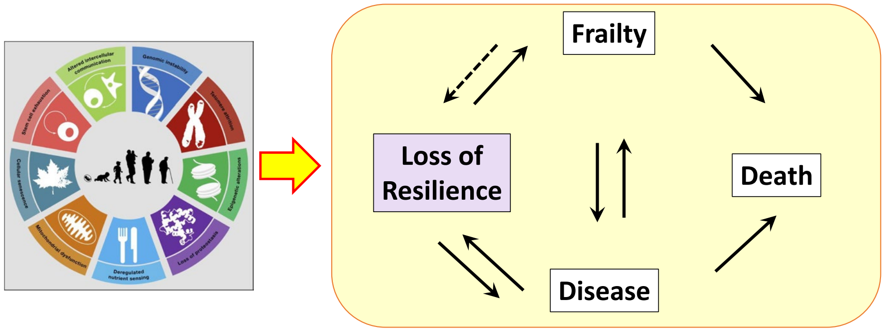

Fig. 1 The interplay between loss of resilience, frailty and age-related diseases. The decline in effectiveness of the processes defined as central to the biology of aging, represented here as the hallmarks of aging, all converge in a loss of resilience. We posit that this is, at the population level, the most common initiator of a cascade of events whereby loss of resilience, frailty and sometimes the appearance of age-related disease all synergize to accelerate the loss of function that eventually leads to death

necessarily causing disease. In that sense, the number of hallmarks of aging is virtually infinite.

It could be argued that there is little practical use for the conceptual framework described by the hallmarks until we develop ways to measure quantitatively and precisely each one of them. This has led to efforts to develop several so-called clocks, of which epigenetic clocks have gathered the most attention [4]. Other efforts at immunological clocks [5], glycomics [6], proteomics [7–9], and others are gaining acceptance as well. However, as mentioned, the list of hallmarks—and therefore potential clocks—is enormous and growing, so trying to catch up and develop a unifying, holistic biomarker of health based on the hallmarks seems like an impossible task. Consider, for example, the best developed clocks: epigenetics. We fool ourselves into thinking that these represent a measure of the hallmark called "epigenetics," but even in the original paper by Lopez-Otín et al. [1], it is clearly stated that epigenetics is not just DNA methylation (the easiest to measure and get sufficient data to develop an algorithm with), but epigenetics also includes histone modifications, chromatin changes, microRNAs, transposable elements, etc. We do not have clocks for these other epigenetic features, and therefore, we don't have a "clock for epigenetics" writ large. Of course, the same can be said about each of the other hallmarks of aging.

Overall, it is naïve to expect that any single measure will recapitulate our entire health status, because while each biological clock might be accurate within its own world, no individual clock can currently provide the dynamics of the entire aging process in the organism as a whole, and therefore, multiple "clocks" would need to be assessed simultaneously. If we consider the previous argument about the number of hallmarks being virtually infinite, this is not a practical approach, and pursuing multiple clocks might not get us to the outcome desired.

Loss of resilience as a unifying outcome of aging biology

We have discussed progressive deterioration of overall health as the defining aspect of the aging process, distinct from disease. In turn, the hallmarks describe prominent mechanisms that, when failing, lead to the manifestations of aging. But how do we connect the two? Here we argue that the so-called hallmarks and their interactions represent the main line of defense or response mechanisms that protect the organism against thermodynamic or other insults, and these defense mechanisms might be infinite. However, we propose that they all converge into a common outcome: a loss of molecular resilience. We will further argue that the loss of molecular resilience serves as a transducer that relays changes in molecular or cellular hallmarks into physiological outcomes as defined by the construct of intrinsic capacities [10]. This view suggests that the rheostat, or most central driver of aging is not to be found among the hallmarks, but rather, it is the loss of systems biology-level interaction among the hallmarks that leads to a loss of resilience, and this is the central, defining characteristic of the aging process, itself leading to frailty, age-related disease, and ultimately death.

To begin, let's clarify that the term resilience is used here within the context of the molecular and cellular changes that occur as a response to a given physical, chemical, or biological stress, as opposed to psychosocial challenges. As such, we are talking about "molecular resilience," that is, the capacity present in every cell in our organism to respond, recover or adapt to a molecular or biological challenge, be it UV radiation, chemotherapy, a virus, or any other physical challenge [11]. Importantly, resilience is an active and dynamic process of the organism interacting with the environment, and this differentiates it from frailty, which is a passive state of physiology.

The focus on resilience might seem arbitrary. After all, while it is clear that in older people the loss of resilience results into a precipitating decline in health, we usually accept that we die of age-related chronic diseases and/or frailty. In fact, there is a clear interplay between resilience, frailty, and disease, whereby any of these processes can exacerbate and accelerate the development of the others, and either the loss of resilience or the development of severe disease can initiate the downhill trajectory towards frailty and death (Fig. 1).

Why focus on resilience then? For one thing, while any given age-related disease only affects a small fraction of the population, loss of resilience—and later, frailty—happens to every individual in virtually all species, usually starting in early adulthood. Perhaps more importantly, at the population level the loss of resilience temporally precedes frailty and age-related chronic disease by several decades, and because of that very reason, unraveling the role and mechanisms of resilience loss will provide an earlier window on which to intervene. As an example, world records in any sports decline with age, in spite of the fact that the practitioners involved are master athletes at the top of their game; but performance at the top of the game is dependent on age [12]. This is depicted in Fig. 2, using world record speed in 100-m dash at different ages. While we recognize that record speed in a sprint is not truly a measure of resilience, we use it here as a proxy since currently there are no widely accepted methods to ascertain resilience (see below). While Fig. 2 shows a decline in record speed already in the 30 s and 40 s, the appearance of frailty is not truly significant at the population level until around 70 years of age. Similarly, the increased incidence of age-related diseases such as coronary artery disease is not evident until a significant loss in resilience has occurred, at which time genes and environment can act upon the "weakened" (that is, less resilient) individuals. Finally, the increase in frailty occurs at a very late age in most individuals, probably due to a strict ceiling effect in its definition [21].

We therefore propose that loss of resilience might represent the composite end-result of molecular declines in any of the multiple processes that we know as the hallmarks of aging. We posit that, due to differences in genetic and environmental clues, loss of resilience might be driven by a different molecular/cellular aging process in any given individual, but since the biological processes represented by the hallmarks of aging heavily interact with each other, the end-result is a generalized loss of resilience, which is independent of the initial trigger. In other words, while some individuals might start their decline because of poor proteostasis, others might do so because of accumulation

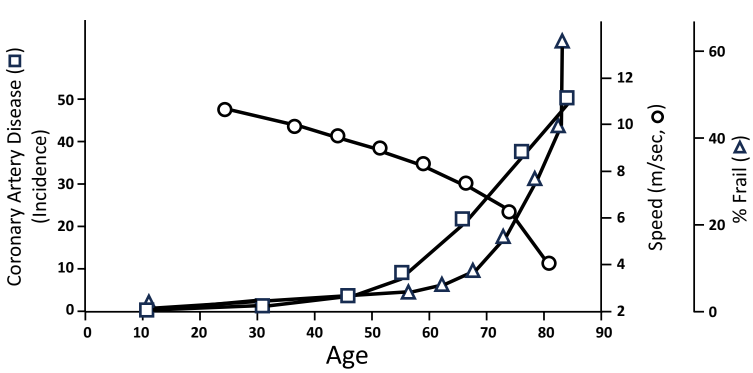

Fig. 2 The timeline of appearance of resilience loss, frailty and age-related disease. Loss of resilience, represented by the world record speed in 100 m races at different ages (circles, ref. [12]) precedes both the appearance of disease (squares, ref. [20]), and appearance of frailty (triangles, ref. [21])

of senescent cells, or a decline in any of the other aging-related processes. However, because of their interdependencies, the end-result is always the same: a decrease in the ability of the organism to respond and recover from a stress, or in other words, a loss of resilience. Furthermore, in addition to each individual displaying different susceptibilities to each hallmark of aging, individuals also differ in the way their organism might respond to the ensuing loss of resilience, so that once the process starts, again there is a variety of physiological process that can be affected, and each individual will be affected by the loss of resilience in a unique manner, again driven by their individual genes and environment. As a result, each individual might present a primary decline in a different functional capacity, depending on their own genetics and environment.

In summary, we propose that a decline in function within any of the hallmarks of aging will result in a generalized decline of the entire molecular and cellular network, leading in all cases to a decline in resilience, which in turn will compromise all aspects of intrinsic capacities, leading to frailty and disease. However, the predominant phenotypic manifestation of this decline, such as decreased mobility or declining cognition, will again depend on the individual's genes and environmental/behavioral exposures. As such, we propose that the loss of resilience represents a nexus or transducer that links the biology of aging to the loss of function and health represented by loss of intrinsic capacities (Fig. 3).

The conundrum: how can we measure molecular resilience in humans?

Loss of resilience is often considered as the other side of the coin to frailty, a relatively well-defined clinical entity for which there are several measurement choices that can provide reasonable predictions of specific outcomes. However, since loss of resilience predates frailty by several decades, this analogy appears to be incorrect, and a more likely (though not yet proven) scenario is that loss of resilience is often what leads to frailty. In that sense, having a methodology to measure resilience might be a valuable tool in our efforts on preventative and individualized medicine.

If we could measure the rate of resilience loss in a 40- or 60-year-old, before the onset of either frailty or disease, this would help us in developing preventative measures for those whose rate of decay is faster than what is expected in the general population. But alas, we do not yet have a toolbox to measure resilience at the molecular level. In fact, since we defined molecular resilience as the ability present in every cell in our organism to respond to physical, chemical or biological challenges, then the challenges to be tested should

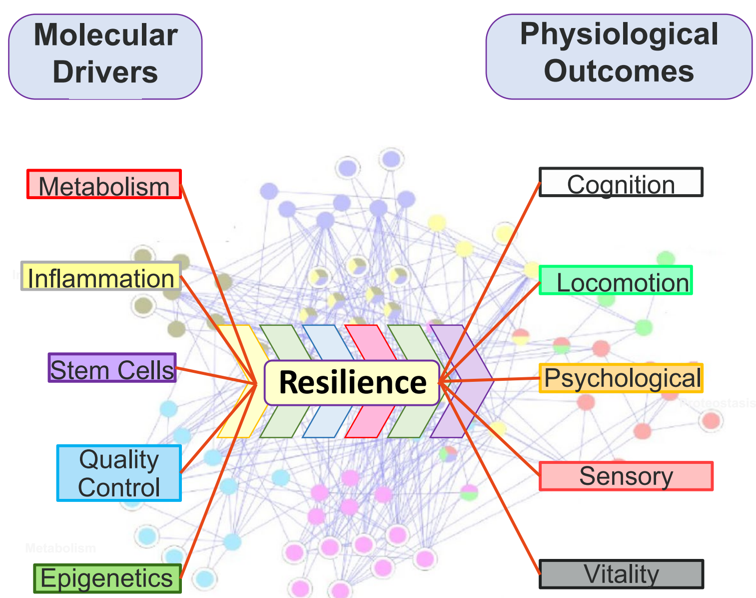

Fig. 3 The central role of resilience as a transducer of information. Loss of resilience acting as the key transducer of information from the molecular and cellular drivers (the hallmarks of aging) to their consequences in terms of physiological (and pathological) outcomes, represented by changes in Intrinsic Capacities

be of quite diverse natures, going from chemical (DNA damaging agents, proteostasis challenges, etc.) to physical (UV radiation, heat, etc.) or biological (viruses, other infectious agents). Of course, applying such challenges to a human would be highly unethical. Although not at the molecular level, alternatives do exist: as a starting point, some work has focused on measuring the future health implications of individual's ability to recover from real-life stresses such as elective surgery [13], chemotherapy [14], or falls [15]. These are "opportunistic" approaches, useful as research paradigms, but they cannot be used as a public health methodology. We also have several measurements of stress at the physiological level, including cardiac stress, vaccinations, V02 max, etc. These tests provide no information on the molecular/cellular mechanisms involved, but an extension of outcome measurements during these tests, to include molecular or cellular parameters might help in our quest. Collection of biological samples/data throughout the testing session, including—critically—the recovery period would be informative not only of the maximal capacity of the system under testing, but it would also inform on the kinetics and dynamics of the response, thus shining light on the overall ability of the system to respond to, and recover from, the challenge. In addition, further omics and/or single cell analyses could shine some light into the molecular processes (including the hallmarks of aging) engaged during both the challenge and the recovery phases. But we really need to develop additional measurements of resilience at more structural levels, from molecules to cells and tissues, that would help to identify causal mechanisms that can be manipulated through clinical or behavioral interventions. One exciting possibility is to use the power of rapidly evolving continuous monitoring devices and big databases to look for the response at the molecular level to everyday real-life stresses such as eating a high fat diet, exposure to high heat or to environmental pollutants, which in principle can provide data on the individual's resilience.

Another alternative could be to challenge cells in vitro. Luckily, the definition above implies that the parameters of interest are intrinsic to every cell in the organism, and therefore could be measured in any cell, and not necessarily in fully differentiated cells such as neurons and cardiomyocytes. We readily acknowledge that this might be an oversimplification, and measuring the resilience of individual, differentiated cells or tissues is likely to be an important goal as well. Unfortunately, we know that while the genetic signature of the individual is retained in cultured cells and iPS cells derived from them, the epigenetic and other characteristics present in the individual donor are not always retained in vitro once cells are put in culture. Thus, the use of cells in culture in this context might be limited to the detection of genetically determined differences in resilience between individuals [16], but changes in resilience due to environmental variables are not certain to be retained in vitro. An attractive possibility is putting cells into organoids, rather than classical 2-D culture, although their utility might be limited by the long time for in vitro maintenance usually required for functional organoids to form. Precision-cut slices might prove more informative [17]. Finally, an attractive alternative might be PBMCs, highly specialized cells that present the advantage of being amenable to being challenged shortly after extraction, and also, being circulatory cells, they suffer less stress from extraction than cells from solid tissues.

Conclusions: the pie in the sky view

Here we argue that loss of resilience is the ultimate determinant of health loss during aging, acting as a transducer for signals from basic cellular and molecular biology, into health outcomes. In this model, a gradual but persistent loss in function in multiple described—or to be described—hallmarks of aging will lead to a reduction in the inventory of compensatory strategies available. This in turn leads to the observed generalized loss in resilience, which is at the root of the increase in frailty and disease susceptibility that often accompany the aging process. Under this scenario, loss of resilience occurs as the net result of a loss in coordination between multiple aspects of aging biology, and this loss of resilience serves as a nexus to transduce the molecular changes into physiological decline. Loss of resilience thus leads inexorably to a loss of balance in the system as a whole, leading to the vulnerability of old age, loss of intrinsic capacities, and ultimately death.

Given that premise, we need to switch the focus of our research on strategies to increase resilience instead of targeting damage removal. For this, it becomes critical for the field to address two interrelated issues: (1) How to accurately and quantitatively measure, at the level of the individual, the resilience of multiple cellular defense and response systems, and (2) Identify what are, at both the population and individual levels, the molecular mechanisms behind the observed loss of resilience with age. This second aspect has been, knowingly or not, at the center of most research into the mechanisms of aging for the past couple of decades, where different animal or cellular models are challenged, for example with toxic chemicals such as LPS [18], overexpression of proteotoxic molecules such as poly Q [19] or multiple other physical, chemical, or biological challenges, and the response is measured as a function of age or genotype in order to identify the transducers or major players in the response. A more challenging issue is how to measure these responses in humans. Important attempts have focused on recovery after natural challenges such as elective surgery [13], chemotherapy [14] or non-planned, accidental challenges [15] which, while more common and relevant to real life, they often lack the "before the incident" data necessary to be fully informative of the person's ability to respond to the challenge. All these studies—preplanned or not—represent opportunistic approaches that cannot be used in the entire population as part of a program of standard preventive care.

Given the central role for resilience proposed here, the ideal challenges necessary to measure it should be non-invasive enough that they can be applied longitudinally in healthy aging individuals. As discussed above, an attractive possibility not yet explored is the use of continuous monitoring devices, where the normal stresses of daily living, both acute, chronic, mild or severe, can be monitored alongside with the changes in parameters such as blood pressure, glucose levels or others. The continuous nature of the measurements ensures that data is available both before, during and after any given natural episode, but unfortunately the data currently collected is not amenable to omics approaches that could be informative by including Machine Learning or Artificial Intelligence approaches.

If measuring approaches can be devised and shown to be both accurate at the individual level, and predictive of future health at the population level, then an ideal scenario for preventive health care would involve measuring molecular/cellular resilience in the entire population at least at two time points before the onset of frailty and disease (say, at 40 and 60 years of age), so as to establish both the "maximal" resilience capacity (at age 40, or earlier) and the rate of loss as a function of time (at age 60). Before we can even start considering such a utopic approach, it is critical that we establish whether resilience really can predict future health. While this correlation is conceptually appealing and seemingly logical, the issue has not been resolved and experimentally shown to be true, and much further research in this area is needed, both in humans and other models.

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Author contributions Both authors contributed equally to the conceptual discussions leading to this work.

Declarations

Competing interest The authors declare no competing interests.

References

1. Lopez-Otin C, et al. The hallmarks of aging. Cell. 2013;153(6):1194–217.
2. Lopez-Otin C, et al. Hallmarks of aging: an expanding universe. Cell. 2023;186(2):243–78.
3. Ferrucci L. The Baltimore Longitudinal Study of Aging (BLSA): a 50-year-long journey and plans for the future. J Gerontol A Biol Sci Med Sci. 2008;63(12):1416–9.
4. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14(10):R115.
5. Sayed N, et al. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. Nat Aging. 2021;1:598–615.
6. Dall'Olio F, et al. N-glycomic biomarkers of biological aging and longevity: a link with inflammaging. Ageing Res Rev. 2013;12(2):685–98.
7. Argentieri MA, et al. Proteomic aging clock predicts mortality and risk of common age-related diseases in diverse populations. Nat Med. 2024;30(9):2450–60.
8. Kuo CL, et al. Proteomic aging clock (PAC) predicts age-related outcomes in middle-aged and older adults. Aging Cell. 2024;23(8):e14195.
9. Lehallier B, et al. Undulating changes in human plasma proteome profiles across the lifespan. Nat Med. 2019;25(12):1843–50.
10. Beard JR, et al. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. BMJ Open. 2019;9(11):e026119.

11. Kirkland JL, Stout MB, Sierra F. Resilience in aging mice. J Gerontol A Biol Sci Med Sci. 2016;71(11):1407–14.
12. Rittweger J, et al. Sprint and endurance power and ageing: an analysis of master athletic world records. Proc Biol Sci. 2009;276(1657):683–9.
13. Walston J, et al. A study of physical resilience and aging (SPRING): conceptual framework, rationale, and study design. J Am Geriatr Soc. 2023;71(8):2393–405.
14. Duchesneau ED, et al. Frailty trajectories following adjuvant chemotherapy and mortality in older women with breast cancer. JAMA Netw Open. 2025;8(3):e250614.
15. Parker DC, et al. Biomarkers associated with physical resilience after hip fracture. J Gerontol A Biol Sci Med Sci. 2020;75(10):e166–72.
16. Murakami S, Salmon A, Miller RA. Multiplex stress resistance in cells from long-lived dwarf mice. FASEB J. 2003;17(11):1565–6.
17. Lyons-Cohen MR, et al. Imaging precision-cut lung slices to visualize leukocyte localization and trafficking. Methods Mol Biol. 2018;1799:237–46.
18. Tarr AJ, et al. The effects of age on lipopolysaccharide-induced cognitive deficits and interleukin-1beta expression. Behav Brain Res. 2011;217(2):481–5.
19. Gidalevitz T, et al. Natural genetic variation determines susceptibility to aggregation or toxicity in a *C. elegans* model for polyglutamine disease. BMC Biol. 2013;11:100.
20. St Sauver JL, et al. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. BMJ Open. 2015;5(2):e006413.
21. Hoogendijk EO, et al. Frailty: implications for clinical practice and public health. Lancet. 2019;394(10206):1365–75.