PNAS OPINION

We need to shift the focus of aging research to aging itself

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Biologists studying aging are rapidly approaching the point where they must face the elephant in the room: They lack any semblance of a consensus on the nature of aging. Image credit: Shutterstock/PeopleImages.com – Yuri A.

The field of aging is at a precipice. Attention and funding are increasingly focused on this area, and exciting, fundamentally important findings are being reported literally every day. As the great promise of targeting aging comes into sharper focus, we are rapidly approaching the point where we must face the elephant in the room: We lack any semblance of a consensus on the nature of aging or, more fundamentally, on the essence of this process. Taking steps to resolve these foundational issues in aging biology will enable us to advance this field to the next level.

What *Is* Aging?

As a field, we claim to study aging—but what, in essence, do we study? What is that most basic, fundamental feature of the process that we call aging? Is it functional decline, damage accumulation, increased mortality rate, continuation of development, increased biological age, decrease in the strength of natural selection, the totality of age-related changes, loss of homeostasis, loss of information, their combination, or something else? After organisms reach adulthood, all of these features seemingly go hand in hand, but their coordination is not perfect, and there must be one underlying, explanatory feature that leads to the others. What is it, and can we truly advance the field without identifying it?

Aging biology is exponentially growing as a field, and talented scientists are designing and carrying out many elegant studies. However, in many ways, we are attempting to construct a building without a foundation. One can see this by the lack of clear answers to some of the most basic questions: When does aging begin? To what extent, if any, is biological age dynamic and potentially

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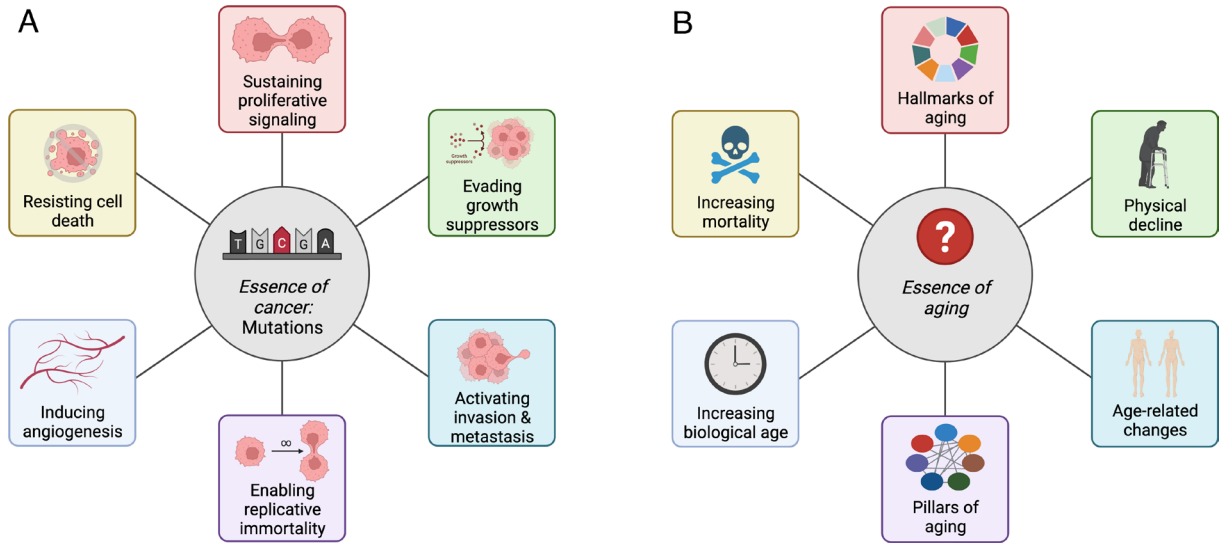

Fig. 1. The essence of aging. (*A*) Underlying the Hallmarks of Cancer is a single essence: mutations (2). Only six of the original hallmarks are represented here. (*B*) Many features characterize aging, and several models have been put forth to conceptually organize these features [e.g., the hallmarks (3) and pillars (4) of aging]. However, the underlying essence of aging remains unclear.

reversible? Which biomarkers are most appropriate to measure biological age, and do any of them actually measure aging directly?

To begin answering these questions and ensuring the future success of this field, we propose two critical concepts on which aging biologists can actively focus their collective attention: the *essence of aging* and the *nature of aging*. To be clear, we are not suggesting that either a formal definition or a unified theory of aging is an immediate need for the field. The essence and nature of aging represent more fundamental concepts, from which we envision that a consensus definition and theory of aging may proceed in the future. In the immediate term, these concepts may serve as building blocks to form the basis of our understanding of aging biology. Developing consensus—or even defining a small number of alternative conceptions of these most foundational aspects of aging—will help to develop approaches that most efficiently address the fundamental questions posed above and, ultimately, will help to target aging directly.

Defining Terms

We define the "essence of aging" as the most basic, essential, explanatory, and causative feature of biological aging. It is the underlying driving force of the manifestations of advanced age, such as frailty, loss of function, and age-related diseases (Fig. 1). Identifying the essence of aging is critical if we wish to study and target aging itself, rather than its later-stage manifestations. Many aging biologists invoke the hallmarks (1, 2) or pillars (3) of aging as a basic starting point for conceptually framing aging biology. However, the essence of aging, in our minds, represents a more fundamental concept underlying these and other characteristics of aging. In the same way that the Hallmarks of Cancer (4) can be reduced to a single essence—mutations—we should be able to, and should strive to, distill a single essence of aging that drives all of the hallmarks/pillars and higher-level manifestations of aging (Fig. 1).

We define the "nature of aging" as the inherent properties and dynamics that characterize aging as a biological phenomenon. The nature of aging is conceptually related to critical outstanding questions in the field, such as the behavior of biological age over the life course; the point at which aging begins; and the extent to which aging of a subset of cells or tissues impacts the aging of surrounding or distant cells/tissues (Fig. 2). The nature of aging is a much broader concept than the essence of aging, but understanding the nature of aging is no less critical to our ability to target this process.

Finally, we note that these two concepts are intimately linked, and we strongly suspect that efforts to study one will inform the other. For instance, identification of the starting point of aging has the potential to bolster or exclude candidates for the essence of aging. Conversely, a consensus on the essence of aging will allow us to more efficiently ask informative questions on the nature of aging to inform future strategies to slow—and potentially reverse—biological aging.

The Next Level

With the potential benefits of targeting aging in mind, we strongly feel that continued operation of this field without a consensus understanding of the most fundamental features of aging itself represents a serious risk. Moreover, moving toward consensus on the foundational issues in aging biology would open the door to many transformative opportunities for the field. Among them:

1. Resolving *unproductive* disagreements: Of course, all fields have internal disagreements and debates. The very nature of the scientific method rests upon testing hypotheses, many of which end up being disproven, and biology is inherently complex. Aging biology is still very much in its infancy, wherein so many of the most basic questions remain open and hotly debated. However, many such debates can often be reduced to differing conceptions of the essence and/or nature of aging. Identifying the most fundamental aspects of aging will allow us to lay a solid

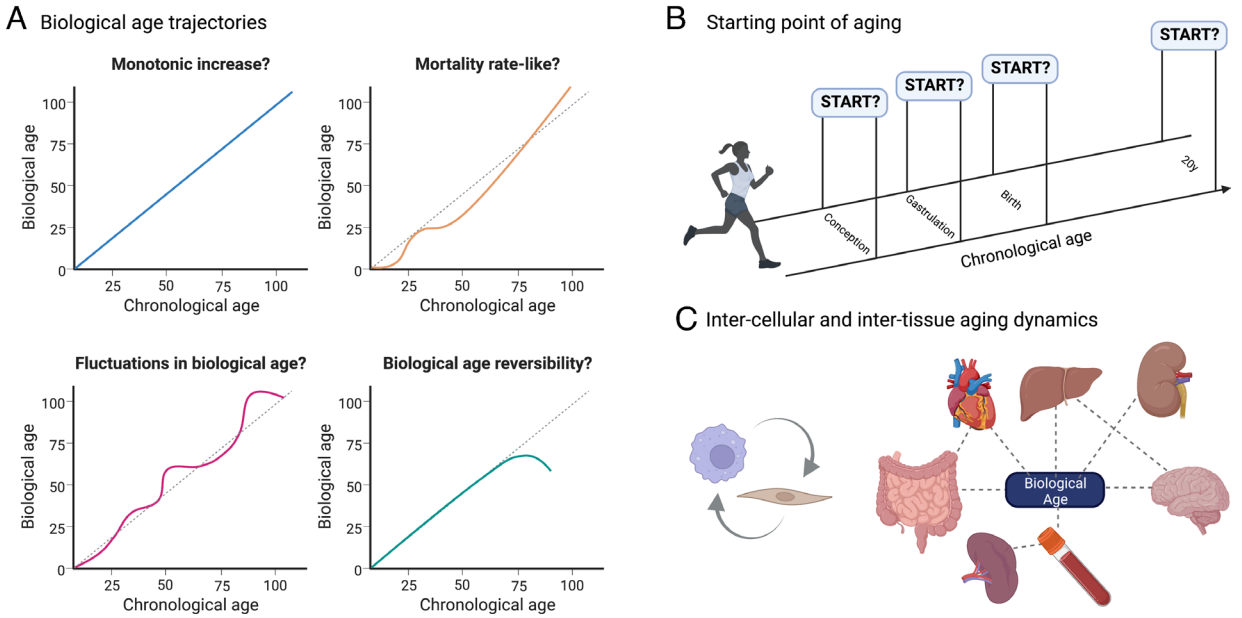

Fig. 2. Examples of critical concepts related to the nature of aging. (*A*) The evolution of biological age over the course of one's life is a poorly understood facet of aging. Several possibilities are illustrated: monotonic increase as a function of age, a mortality rate-like trajectory, fluctuation over the life course, and potential reversibility. (*B*) The starting point of aging is similarly unclear currently. Pinpointing the starting point of aging may help explain aging and decide when to initiate antiaging interventions. (*C*) The extent to which biological age is influenced by cell nonautonomous effects and intertissue communication is also an outstanding area of inquiry. Understating these aspects of aging will be critical for the application of interventions that feature differential efficacy in particular cell populations or tissues.

foundation of knowledge for the field, enable us to resolve open debates, and propel our scientific inquiries further.

2. Establishing fruitful collaborations: Combining diverse expertise often produces a product that is greater than the sum of its parts. The aging field also benefits from a unique integration between academic and industrial scientists. Nevertheless, aging biology, in general, remains a rather siloed field. Greater collaboration and cross-fertilization of expertise will be needed to tackle the complexity of aging. If an agreed-upon target to study is identified and understood, powerful collaborations, particularly those with experts in complementary fields, may be more readily established.

This field is poised to have a positive impact on aging people and on society as a whole; that goal is too important to risk by continuing to operate without consensus on the most fundamental aspects of aging: its essence and nature.

3. Clear communication about the importance of aging biology to the broader society: One point on which most aging researchers *do* agree is that targeting the aging process itself has the potential to prevent or mitigate many of the diseases of aging, an idea crystalized in the Geroscience hypothesis (5). With this in mind, it's hard to understand why 60% of National Institute on Aging funding is dedicated, by statute, to a single disease (Alzheimer's), while this same disease and many others would likely benefit from approaches that target aging itself. We suspect that this apparent cognitive dissonance is fueled by our field's lack of success in communicating to the US Congress and the broader society even the (arguably) single idea on which we do share a broad consensus. This reflects a deeper shortcoming: our lack of ability to speak as a field with a unified voice. This is needed to communicate to regulatory agencies, to elected officials, and to society at large about the centrality of aging as a risk factor for the diseases of aging and the great promise of improving health by targeting aging itself. Establishing consensus on what we are actually studying will be pivotal to developing such a unified voice.

4. Ability to distance from unsubstantiated antiaging claims: This field suffers from claims of antiaging effects in humans. We need to make it abundantly clear that no scientifically proven antiaging or age-reversing drugs or interventions yet exist for people with healthy lifestyles. This is not to say that such interventions cannot be developed. We know of more than 10 reliable interventions that extend the mouse lifespan, and scientists have extended the lifespan of nearly every model organism that they have targeted (6–8). Coordinated distancing from unsubstantiated antiaging claims will ensure our future credibility for when bona fide antiaging interventions for humans are identified. Consensus on what aging is and what it is not will be key to achieving this goal.

5. Prioritization of the most effective geroprotective interventions: As we continue efforts to identify and validate interventions that target aging in humans, we must ensure that the benefits of aging science are accessible and equitable. To achieve this goal, the field should prioritize development of the most broadly efficacious interventions targeting aging. Consensus on the essence of

aging and deeper understanding of its biological nature can directly support this goal.

Promising Outlook

It is extremely exciting to work at the cutting edge of a burgeoning field like aging biology. The great promise of improving lives through targeting the aging process itself is a major source of inspiration for pursuing such work. This field is poised to have a positive impact on aging people and on society as a whole; that goal is too important to risk by continuing to operate without consensus on the most fundamental aspects of aging: its essence and nature. Many existing aging studies have the potential to contribute to our understanding of these features, and we hope that they will be more explicitly discussed by researchers in the future. By defining our target, we will be better able to design future experiments; communicate with each other within the field and with the broader society; and protect aging biology from being perceived as any less than the important field it truly is. As such, we must strive to grapple with these critically important concepts.

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