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The Origin of Aging: Imperfectness-Driven Non-Random Damage Defines the Aging Process and Control of Lifespan

Vadim N. Gladyshev
Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA

Abstract

Physico-chemical properties preclude ideal biomolecules and perfect biological functions. This inherent imperfectness leads to the generation of damage by every biological process, at all levels, from small molecules to cells. The damage is too numerous to be repaired, is partially invisible to natural selection and manifests as aging. I propose that it is the inherent imperfectness of biological systems that is the true root of the aging process. As each biomolecule generates specific forms of damage, the cumulative damage is largely non-random and is indirectly encoded in the genome. I consider this concept in light of other proposed theories of aging and integrate these disparate ideas into a single model. I also discuss the evolutionary significance of damage accumulation and strategies for reducing damage. Finally, I suggest ways to test this integrated model of aging.

An age-old question

Defining the biological basis of aging and control of lifespan is one of the greatest challenges in biology [1,2]. Aging is often viewed as an accumulation of changes over time that renders organisms more likely to die. However, neither the nature of these changes nor the causal relationships in aging are understood, and many related fundamental questions remain unanswered. Has a process that makes organisms more vulnerable and more likely to die evolved? Does it have purpose? What is the cause of aging? What are the associated mechanisms? Can aging be stopped or postponed? How do genomes define lifespan? How is lifespan adjusted during evolution and in response to dietary interventions? Numerous aging theories and concepts have been advanced over the years, many of which are difficult to reconcile, and none of them seem to adequately explain all aspects of the aging process. Here, I describe a different perspective, compare it to previously advanced ideas, and suggest that it allows integration of diverse theories into a single concept of aging.

Heterogeneity and imperfectness of biological systems

Accumulation of molecular damage that arises through the imperfections in the molecular machinery of life has long been considered key to the aging process. It is not clear, however, how this damage is generated, whether it is generated purposefully, why it cannot be completely removed from cells, and whether it is stochastic. It is also not known whether

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Corresponding author: Vadim N. Gladyshev (vgladyshev@rics.bwh.harvard.edu).

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damage causes aging or is simply a bystander generated with no influence on the process. Although the idea that cumulative damage causes aging [3] is viewed by many as a truism, nearly every aspect of this idea is questionable, with many researchers discounting damage as a relevant factor altogether [4].

To understand the origins and impacts of damage as they relate to aging, consider an enzyme that converts substrate S_1 to product P_1. Since enzymes are promiscuous with regard to substrates and products [5,6], if an enzyme converts 99% of S_1 to P_1 (being a very impressive catalyst), and the remaining 1% of S_1 to a by-product B_1, what happens to this and other minor reaction products (e.g., generated if the enzyme reacts with S_2 generating B_2 or makes other by-products from S_1)? Significant flux through this enzyme would rapidly generate significant amounts of certain byproducts, requiring cells to develop a mechanism to handle them.

Extending this notion to all enzymes in the cell, what would happen to all this damage? Enzymes are inherently limited in their capacity to catalyze specific reactions with maximal yield because they are built from only 20 common amino acids (and a few cofactors) and exist in multiple conformations. A significant fraction of enzyme molecules in the cell contain the wrong amino acids due to errors in transcription and translation. Imagine now that this concept applies to all other cellular macromolecules and metabolites - this biological imperfectness will necessarily lead to the generation of myriad by-products and errors [7]. How could cells possibly deal with so many unwanted products?

The imperfectness model

I suggest that cellular life involves (i) the generation of damage as an inevitable consequence of the imperfectness-driven metabolism, and (ii) the removal of damage when it is cleared or diluted, or when cells are renewed (Box 1) [7]. It is important to consider this push-pull relationship from an evolutionary perspective. If a cell makes only a few molecules of a certain damage type during its lifetime, this damage will not be “visible” to natural selection, and no genes will evolve to protect against it. Neither will protection evolve against other minor damage types each represented by several molecules. Moreover, it would be impossible for the cell to deal with all damage forms, as damage is produced by every reaction and interaction in the cell (because all of them are imperfect) and at every level, from the smallest molecules to cells and organs. Therefore, the number of damage forms will always be greater than the number of protective and repair systems.

Box 1

Features of the imperfectness model of aging

- **i.** Cause of aging. Imperfectness (and conceptually related heterogeneity, promiscuity, infidelity) of biological systems represent the ultimate cause of aging.
- **ii.** Imperfectness of biomolecules. All biomolecules are inherently imperfect as dictated by their physico-chemical properties, e.g., they are built from a limited set of building blocks by error-prone processes.
- **iii.** Damage from each biomolecule. The by-products and other damage forms are generated by each and every macromolecule and at all levels, from small molecules to cells.
- **iv.** Damage exceeds the ability to remove or repair it. Damage forms are too numerous to be cleared up, i.e. there is a greater number of damage forms than possible protective systems.

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v. Inevitable damage. Biological imperfectness is the reason the damage is inevitable.

vi. Cells clear severe damage and ignore the rest. Damage that decreases fitness is removed by protection systems, whereas slightly deleterious, mild damage is invisible to evolution and cannot be protected from. Instead, cell division and renewal allow dilution of this damage.

vii. Damage overload in non-renewable cells. The occurrence of non-renewable cells and structures leads to eventual damage overload.

viii. Non-random damage. Damage is largely non-random: it is determined by composition and rate of metabolism, e.g., an enzyme will generate a specific product and a set of specific byproducts, and not just any damage forms.

ix. Damage is genetically encoded. Damage and the rate of its generation are indirectly encoded in the genome (through biomolecules that make damage when carrying their direct functions).

x. Ever changing cumulative damage. Changes in metabolism (e.g., during speciation, changes in diet or environment, or during aging itself) will lead to the generation of different forms of damage and at different rates.

xi. Origin of aging. The damage generation/clearance/dilution strategy operated ever since the first cellular organisms and is rooted so deeply in metabolism that it is an essential part of cellular life.

xii. Mortal and immortal organisms. Organisms may be theoretically immortal if they achieve full equilibrium in cumulative damage, whereas organisms with post-mitotic, non-renewable cells and structures are necessarily mortal.

xiii. Evolution and aging. The cause of aging is not subject to natural selection.

xiv. Evolution of lifespan. Evolution can influence lifespan (and other life-history traits) by optimizing metabolism, thereby adjusting the patterns and rate of accumulation of cumulative damage.

Although only the more severe types of damage will provide a substrate for natural selection to act on, damage can also be dealt with by cell division. This way, cells can remove severe damage with protection systems and essentially ignore inabundant, slightly deleterious, milder damage forms, which will be diluted when cells divide. This strategy accommodates imperfectness in biological systems and has been operating for billions of years, defining all cellular life as we know it. It is rooted so deeply in cellular life that it became a part of life itself [7], similar to the “frozen accident” of the genetic code [8]. However, when biological innovation led to the development of multicellular organisms with fully differentiated, non-renewable cells (such as neurons in mammals) and irreplaceable structures (such as the skeleton) as well as to unicellular cells that asymmetrically divide or produce daughter cells from within the old cells (such as the budding yeast), the consequence was aging. In the case of yeast, the daughter cell relies on all newly synthesized cellular components, whereas most of the damage accumulated in the mother is blocked from entering the daughter. Inheritance of the damage accumulation/dilution strategy from unicellular organisms meant that non-dividing cells would eventually reach the stage of damage overload and die.

Environment also contributes to cumulative damage, but it is not a major factor (e.g., humans, domestic cats and house mice living in a similar environment have widely different lifespans). Although most damage forms considered in isolation would not result in measurable effects on fitness, together they decrease fitness over time. Moreover, individual

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damage forms are intimately linked to each other and cumulatively affect the cell that makes them. For example, a damaging posttranslational modification of an enzyme may affect its conformation and catalysis, influencing its catalytic efficiency, degree of promiscuity and macromolecular interactions. In turn, these altered functions would affect other cellular components, propagating the damage.

In contrast to the prevailing view in the aging field, I suggest that cumulative damage is largely not random, and that it is determined by the specific metabolic set up of a cell/organism. That is to say, just as the balance of metabolism is ultimately encoded in the genome, so is the damage that inherently arises from metabolic processes. Indeed, each enzyme will produce specific forms of damage (rather than any damage), each damage form will exhibit preference with regard to interaction with cellular components, and changes in the metabolic state of a cell will predictably change its damage composition. Damage will be shaped by the number of processes that generate it and by the flux through these processes. With the same energy expenditure, the use of fewer metabolic processes will generally produce fewer damage types, requiring fewer protective systems, compared to the situation when energy expenditure is distributed across many processes. In other words, a more direct, stable, optimized generation and use of energy will generate less damage. Such streamlined metabolism may be accomplished, for instance, by using fewer regulatory systems and futile enzyme cycles, decreasing complexity of metabolism, and compartmentalizing it. This can be conceptualized by updating the famous analogy likening aging to a car that eventually rusts and stops running. Consider instead that it is the damage to the car generated in the process of driving that correlates best with the lifespan of that car – with the same energy expenditure a car driven only on empty highways will outlast one driven in a city, where it will need to often change speed, turn, stop, and reverse.

Cumulative damage will be primarily defined by genes encoded in the genome (with some contribution from environment, diet and a plethora of other factors), and the damage generated in different species will be related according to phylogeny, changes in life-history traits and lineage-specific adaptations. Just as no two humans are the same, identical cumulative damage patterns do not exist. Cells with similar genotypes and environmental conditions will be characterized by similar damage forms, yet some damage will be unique to each cell. Moreover, damage in a cell/organism changes over time and influences metabolism, further complicating the cumulative damage landscape. Thus, as one defines cumulative damage it is important to consider both damage composition at any given moment and damage accumulation over time.

Can inevitable, non-random damage generation be adjusted during evolution? Natural selection acts on processes that directly or indirectly affect generation of all damage and removal of severe damage (e.g., in response to hazardous environments, changes in availability of resources, predation, etc.). Thus, although imperfectness inevitably leads to damage, which drives aging, the type and rate of damage accumulation are genetically controlled. Damage is not the cause of aging (imperfectness is) but rather an instrument of evolution to control life-history traits, thereby regulating lifespan. It is unclear if lifespan is the trait directly selected during evolution, but it can be adjusted as a component of life-history of species. For example, selection for larger body mass to avoid predators may lead to an increase in lifespan. Since the imperfectness-driven cumulative damage is a function of opposing genetically-controlled processes that increase damage (activity of metabolic processes, influence of environment) and decrease it (damage clearance by protective systems, damage dilution by cell division and cell renewal), several strategies may be predicted to affect cumulative damage (Box 2).

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Box 2

Implications for the approaches that affect lifespan

Hypometabolism and metabolic reprogramming

Decreasing the rate of metabolism, which may be directly affected by temperature and flux through metabolic pathways, can extend lifespan. For example, the lifespan of fruit flies and nematodes is extended at lower and shortened at higher temperatures. However, energy expenditure is not necessarily proportional to cumulative damage. It may be accompanied by a more optimized use of energy, thereby decreasing the diversity of damage forms. Physical activity may have this effect. This may also be reflected in differences among cell types (e.g., long-lived cells such as neurons and cardiomyocytes may produce less damage than some other cells due to a more optimized metabolism).

Damage dilution

Unequal distribution of damage between two daughter cells, or dilution of damage by cell division can extend lifespan. This strategy is used in the budding process in the baker's yeast and iPS-type cell reprogramming, which reset the aging clock.

Damage maintenance

Damage can be decreased by increased activity of maintenance systems, e.g., DNA repair, proofreading mechanisms during RNA and protein synthesis, protein and metabolite repair pathways, antioxidant and detoxification systems, and autophagy. However, maintenance can only deal with some damage forms and comes at a cost, as these systems themselves generate other damage forms.

Lifespan extension by dietary intervention

Caloric restriction extends lifespan in a variety of organisms. It may change the metabolic state of a cell/organism, thereby affecting the rate and forms of damage generated. For example, yeast responds to caloric restriction by activating respiration, which generates energy more efficiently, even though the damage from respiration *per se* may be higher [28]. Lifespan can also be extended by rapamycin [29], metformin and several other compounds. Rapamycin acts by inhibiting mTOR, which alters the metabolic state and slows down metabolism, thereby changing the damage landscape.

Decreased mortality in late life

One paradox of aging is the decreased mortality in late-life [30]. From the imperfectness perspective, two factors may be relevant. First, any population will consist of sub-cohorts differing in cumulative damage. The individuals with more severe damage will be eliminated earlier, leaving those with less severe damage. Second, cumulative damage will feedback to metabolism, decreasing its rate in late life, thereby decreasing the rate of damage generation. Thus, the paradox of aging subsiding in late life can be explained from both population and individual organism levels.

Organisms that do not age

The imperfectness model suggests that some organisms, even animals, may theoretically be immortal. Damage accumulation may be confined by balancing damage by cell division or replacement of old somatic cells with new cells. For example, some multicellular organisms, such as hydra and planaria, possess efficient cell renewal strategies when growing asexually. Whether they are truly non-aging is unclear, but this possibility is not excluded by the model. Unicellular organisms with truly symmetric

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divisions do not age, whereas asymmetric division, even in bacteria [31], will lead to aging.

Organisms that age

The presence of post-mitotic non-renewable cells (e.g., neurons) and structures (e.g., skeleton) are hallmarks of aging. Non-dividing cells will necessarily accumulate damage and eventually die. Changes in the reproductive mode (e.g., sexual versus asexual) and environment may convert certain non-aging organisms into aging ones, and *vice versa.* These considerations blur the definition of an aging organism, but pinpoint the origin and disappearance of the aging process.

Relationship of the model to other aging concepts

Programmed aging

The model of programmed aging, first formulated by August Weismann in the 19th century, proposes that aging is a purposeful program and that the death of older individuals in the population benefits subsequent generations [9]. The model implies that this altruistic plan has evolved and been maintained for purpose (e.g., to benefit future generations), involves certain genes, and can possibly be cancelled or postponed [10]. By contrast, I suggest that the driving force of aging (imperfectness) applies to all genes and cellular processes. Imperfectness is a fundamental property of chemical and, therefore, biological systems that neither has evolved nor has purpose. Aging can only be viewed as programmed in the sense that it involves all genes and the entire metabolism, and is therefore a direct consequence of life. But this is not a program (unless the program is life itself), it was not designed for the purpose of aging, and it cannot be cancelled in living organisms (but see Box 2 for organisms that may not age).

Hyperfunction

The hyperfunction aging model suggests that aging is a consequence of over-activity of processes, which continue after the completion of development, and involves an imbalance between cell growth and cell cycle control signals [4,11–13]. Hyperfunction resembles programmed aging, although it has not evolved for the purpose of aging, so it has been referred to as quasi-programmed aging. Damage accumulation is explicitly excluded from the theory as a causal or relevant factor (i.e., it may accumulate but is considered irrelevant to the aging process because hyperfunction kills an organism first) [4,14]. What is viewed as hyperfunction and continued development (and any other aspects of dysregulation of cellular processes), however, represent the secondary manifestations of aging that can be easily understood in terms of cumulative damage, especially in cells that are metabolically active, yet unable to divide. What the hyperfunction theory considers as aimless continuation of growth and development is in fact metabolism that sustains life, but inevitably accumulates damage, causing dysfunction. The hyperfunction aging model implies that tight regulation of the developmental program during adulthood may stop or significantly delay aging. However, in metabolically active, non-dividing cells, damage would inevitably accumulate, whether developmental programs are active or completely blocked. Some developmental processes do stop (e.g., consider human height), and the inability to halt other developmental processes may ultimately be caused by imperfectness. Since cumulative damage is indirectly encoded in the genome through the activities of directly encoded cellular components, aging does come out as quasi-programmed, even though this quasi-program is not what is meant by the hyperfunction concept.

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Evolutionary theory of aging

According to this model, aging is a consequence of decline in the force of natural selection that occurs late in life, after successful reproduction [15]. The theory proposes that mutations improve genes beneficial in early life, whereas these mutations may inactivate genes that are beneficial later in life. It is further proposed that the genes benefiting young organisms will be selected for even if they are harmful at older ages [16,17], leading to the concept of antagonistic pleiotropy. However, the model presented here argues that, over time, the contribution of any gene to cumulative damage will outweigh its beneficial effect, regardless of whether this benefit declines, increases or is constant throughout life. Thus, genes appear to exhibit antagonistic pleiotropy because they both benefit organisms at any time and contribute to cumulative damage over time. Moreover, this argument is not limited to genes and mutations and applies to all metabolites, macromolecules and other purposefully used molecules in the cell. For example, the use of transition metals, such as copper and iron, as protein cofactors is selected during evolution, but they also significantly contribute to cumulative damage due to their reactive nature. Their use made organisms more competitive, but also contributed to accumulation of damage over time. Respiration that produces damaging reactive oxygen species is another example of antagonistic pleiotropy. Overall, the imperfectness model offers a molecular explanation for the evolutionary theory by reformulating it into an interplay between biological functions (which do not change) and their contribution to damage (cumulative over time).

Disposable soma

The existence of trade-offs between different phenotypes and components of fitness is viewed as a key feature of evolutionary biology. The disposable soma theory proposes that organisms balance resources that they invest into reproduction and somatic maintenance, resulting in trade-offs between somatic repair and reproduction [18]. For example, a more significant investment in reproduction is thought to decrease investment in maintenance thereby shortening lifespan, whereas reduced reproduction allows redistribution of resources towards protection, thereby extending lifespan. Like the imperfectness model, the disposable soma theory considers damage accumulation key, but there are also critical differences between the two models. First, our model does not require the trade-off between somatic repair and reproduction, which may be explained by the fact that reproduction is a metabolically demanding process that generates damage (i.e., lower reproduction may generate less damage extending lifespan). Maintenance cannot be 100% efficient not because some resources are used for reproduction, but because of biological imperfectness. Second, whereas the disposable soma theory envisions somatic maintenance as a chief genetic factor that determines lifespan, I suggest that lifespan is genetically controlled by a combination of factors that contribute to damage generation and clearance. Understanding the balance of these factors could explain why some treatments and mutations extend lifespan without reducing reproduction [19,20]. Maintenance can only deal with more severe damage, while there is no protection against milder damage. Disposable soma's focus on maintenance, as opposed to all processes that contribute to cumulative damage, also leads to differences in predictions. For example, with regard to damage, the disposable soma theory places cancer and aging on opposite sides of a see-saw [21], whereas our model places them on the same side (Box 4). Third, the disposable soma theory suggests that damage is random, whereas I propose that it is not. Fourth, the disposable soma theory considers limited metabolic and energy resources that are partitioned among various processes, whereas I propose that it is the limited capacity for withstanding damage that is at the heart of the aging process. Overall, the imperfectness model opposes excessive focus on maintenance, the idea of limited resources, the idea of random damage, and a fundamental role for the trade-off between reproduction and maintenance.

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Box 4

Insights into age-related diseases

Many diseases associated with advanced age have a genetic component. However, extensive efforts to understand the genetics of complex diseases revealed a relatively low inheritance that accounts for only a fraction of disease incidence. Whereas many Mendelian diseases appear at any age, complex human diseases, such as cancer, diabetes and neurodegenerative diseases primarily arise at an advanced age. Central metabolism has almost invariantly been implicated in these diseases. For example, cancer incidence increases with adult age, highlighting the fact that this is a disease of aging [32]. Cancer is driven by mutations that inactivate tumor suppressors and activate cell growth pathways. However, besides a few driver mutations cancer cells also accumulate tens of thousands of passenger mutations. By randomly targeting genes, regulatory regions and other functional areas of the genome, these mutations adversely affect cancer cell metabolism, leading to increased generation of damage. To compensate for these vulnerabilities, cancer cells must divide to dilute their damage. However, the collateral damage does expose vulnerabilities which can be therapeutically targeted [33,34]. Thus, cancer is particularly dependent on cell division. Although most damage forms in cancer cells can be diluted, damage in the form of mutations is preserved in the DNA, providing readout of the damage as well as an opportunity to understand it and use this information in therapy. Another characteristic feature of cancer is its dependence on glycolysis to generate energy (the Warburg effect). It lowers efficiency of energy utilization, but allows cancer cells to grow faster. This situation may be similar to the baker's yeast that uses anaerobic fermentation even under aerobic conditions when glucose is plentiful.

Oxidative damage

This model, also known as the free radical theory of aging, proposes that reactive oxygen species damage biomolecules, causing aging [22]. While oxidative damage may contribute to aging, placing emphasis on just one damage type limits its relevance, and it does not represent the ultimate cause of aging (but represents proximate cause). It may be more relevant to regulating lifespan under certain conditions, but irrelevant under other conditions. Aging would still occur in the absence of oxygen, and even if there was no such thing as reactive oxygen species. For example, yeast cells grown under anaerobic conditions not only age, but they have a shorter lifespan than cells grown under aerobic conditions [23]. The oxidative damage theory, like any other concept that considers a single class of damage, requires reformulation.

DNA damage

This theory proposes that damage to DNA causes aging [24]. DNA is the only molecular species in the cell that cannot be renewed, and DNA damage clearly contributes to aging [25]. Again, however, DNA damage represents only a subset of cumulative damage. For example, in yeast, daughters of old mother cells have a shorter lifespan, but the lifespan is restored in granddaughters [26]. It appears that much of the damage accumulated in old mother yeast cells is transferred to their daughters, but it is diluted in subsequent generations. The imperfectness model encompasses this theory, while not placing emphasis on any one type of damage.

Damage-centric theories of aging

Damage-centric models, from simpler ideas such as wear and tear (essentially the classical rusty car analogy) to the advanced concepts that are integrated with evolutionary models,

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place cumulative damage in the center of the aging process [1], but they view damage as random and do not explain why damage is inevitable, why it is generated and why it cannot be fully removed. These models do not distinguish between severe and mild damage forms, do not recognize the primacy of genotype in defining damage, and do not logically separate the cause of aging from the control of lifespan. They do not consider damage dilution as a strategy to dilute the damage for which there is no protection and do not view different metabolic states as associated with unique patterns of damage accumulation. Finally, these theories posit that there are many causes of aging, but in fact each damage theory refers to a specific mechanism contributing to the aging process rather than the cause of it. The imperfectness-driven processes would result in aging even if each of the individual damage-centric mechanisms discussed in the literature, or all of them together, are eliminated.

Rate of living

This model proposes that various species have a relatively constant level of total metabolic output over lifetime. Therefore, organisms with faster metabolic rates age more rapidly. This model is consistent with correlations within mammals, but does not have a clear molecular underpinning and fails to explain why certain organisms with high metabolic rates have longer lifespans than similarly-sized animals (e.g., bats versus mice, birds versus mammals, etc.). It was shown that metabolic rate does not correlate with lifespan when the metabolic rate is normalized to body mass [27]. The rate of living model utilizes energy expenditure, whereas I suggest that the measure should be how much damage is produced by expending a certain amount of energy. This damage will differ depending on the metabolic design of the system. For example, a single enzyme utilizing 1000 ATP molecules will produce fewer types of damage than 100 enzymes that use 10 ATP molecules each. Although energy expenditure will be the same, the damage generated will be different. More generally, a more direct, stable, streamlined generation and use of energy will produce less damage. Thus, the rate-of-living concept should be reformulated by shifting focus from energy expenditure to how much damage is produced with the energy resources given.

Concluding comments

Researchers have traditionally ignored imperfectness, infidelity, promiscuity and heterogeneity of biological systems, mostly for two reasons: (i) lack of experimental approaches to reliably detect, distinguish (e.g., from functional cellular components) and analyze by-products of metabolism and other unwanted products; and (ii) a reductionist approach that focuses on individual cellular components and systems (genes, proteins, metabolites, pathways, etc.), their primary functions and regulatory mechanisms. However, recent advances in high-throughput technologies, especially sequencing, proteomics and metabolomics, may finally allow analyses of this gray side of metabolism, including by-products and other damage forms, their properties (e.g., identity, number, synchronization, age-dependent diversity, causal roles in the aging process) and the mechanisms that are responsible for their production and clearance, as well as metabolic reprogramming and regulation over evolutionary timescales that control cumulative damage. Life has a chemical basis, and regardless of how complex biomolecules and biostructures are, chemical rules do not disappear when biological and physiological processes are considered. Accepting imperfectness as a general feature of biology and a fundamental mechanism that applies to each and every cellular process may bring a paradigm shift in how we view cellular life and death. This mechanism defines the inevitable source of damage, explains its non-random nature and regulation during evolution and as organisms age, shows that aging is non-programmed (yet indirectly encoded in the genome), and accounts for biological trade-offs and molecule-to-molecule, cell-to-cell and other variabilities in biological systems. This concept challenges the textbook models of perfect macromolecules, pathways, cells and organisms (which in reality do not exist), explains many experimental observations,

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integrates diverse aging theories into a single model, and shows the origin of aging and its place in biology. With the imperfectness-driven non-random damage-mediated aging process, causal relationships in cell and organism life emerge, providing opportunities for understanding fundamental biological mechanisms and using this information in biology and medicine.

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Box 3

Testing the model of imperfectness-driven non-random damage

What good is a model if it cannot rigorously be tested? The challenge is that experimental analyses of the imperfectness-driven non-random damage must be completely different from the analyses of large and direct effects that are commonly examined by investigators. Like evolution that acts via large numbers of small-effect changes in numerous genes leading to changes in phenotypes, damage forms act in combination, but their effects are difficult to detect when each is examined in isolation. These small-effect damage forms widely differ in their molecular composition and consequences, and are fundamentally different from the large effects of lifespan-affecting dietary interventions (caloric restriction, rapamycin treatment, etc.) as well as mutations in genes and pathways (insulin signaling, sirtuins, TOR pathway, etc) that are commonly studied by researchers in the field of aging. Nevertheless, we suggest that one can adapt certain new technologies and develop experimental approaches to test the concept.

The idea of imperfectness-driven non-random damage leads to a number of testable predictions. For example, damage forms must be numerous (there should be more damage forms than purposely used metabolites in old cells/organisms) and must increase during aging. Cumulative damage should also increase in diversity as a function of age, and there should be some degree of synchronization in damage accumulation as the organism ages. In addition, cumulative damage should directly affect cell/organism fitness, rather than be a bystander not influencing cellular processes directly. Another prediction is that most components of cumulative damage will be mildly deleterious and inabundant. Finally, interventions that extend lifespan should change the landscape of damage (different pattern of accumulating damage) and decrease its rate of accumulation with age. These properties can be directly analyzed in experimental systems ranging from individual enzymes to pathways, cells and organisms.

Sensitive high-throughput methods, such as sequencing, proteomics and metabolomics as well as single cell approaches should be instrumental in detecting, quantifying and characterizing molecular damage. Although many chemical forms represented by only a few molecules in the cell will be inaccessible, the bulk of the damage will be detectable. For example, metabolite profiling methods enable detection of tens of thousands of molecular species, so focusing on those least abundant may allow a direct test of predictions with regard to properties of the age-related damage. In addition, sequencing allows detection of individual mutations at the level of single-cell genomes and transcriptomes. Finally, changes in the metabolic set up of species, organs and cell types, as well as metabolic adjustments in response to genetic manipulations, dietary interventions and environmental conditions, may be reflected in gene expression, protein expression and metabolite patterns.