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Ontogenetic Permanence of Non-Renewable Biomechanical Configurations in Homo Sapiens Anatomy

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Abstract

Aging in biological organisms is intricately linked to the accumulation of damage in long-lived irreparable structures, which remain unchanged throughout life. These structures include lens proteins (crystallins), DNA of postmitotic neurons, mitochondria of cardiomyocytes, tooth enamel, and centrioles of stem cells. Formed in the early stages of ontogenesis, they serve as "entropy accumulators"—a thermodynamic measure of molecular disorder. The impossibility of their replacement is dictated by evolutionary compromises: for instance, the stability of centrioles is crucial for the asymmetric division of stem cells, yet their selective inheritance results in the transfer of damage to progeny, thereby accelerating tissue aging. The accumulation of oxidized proteins, DNA mutations, and dysfunctional organelles disrupts homeostasis, triggering neurodegeneration, cataracts, and heart failure. This article examines the mechanisms underlying the damage to these structures, their role in age-related pathologies, and promising therapeutic strategies, including senolytics, CRISPR correction, and biomimetic materials. Special emphasis is placed on centrioles as key regulators of cellular entropy: while their stability supports tissue regeneration, defect accumulation leads to gene expression disruption and contributes to oncogenesis. Understanding the balance between longevity and vulnerability in irreparable structures opens new avenues for combating aging through targeted entropy management.

Keywords: Aging, Entropy, Irreparable Structures, Centrioles, Mitochondria, Crystallins, Neuronal DNA.

Introduction

Aging is a universal biological process characterized by a progressive decline in an organism's functional capacity and an increased risk of disease. Despite considerable advances in aging research, many aspects of this process remain subjects of intense scientific debate. One of the key concepts explaining aging is the entropy accumulation theory—a thermodynamic measure of disorder, manifesting in biological systems through molecular, organellar, and tissue damage (López-Otín et al., 2013). The body continuously counteracts entropy by renewing cells and structures: liver hepatocytes regenerate every 150–200 days, epidermal skin cells every 2–4 weeks, and erythrocytes every 120 days (Sender et al., 2016). However, certain unique long-lived structures do not undergo renewal throughout life, effectively becoming "reservoirs" of molecular damage. These irreparable elements, from lens proteins to postmitotic neurons, play a critical role in the development of age-related diseases, forming the basis for neurodegeneration, cataracts, and heart failure (Truscott, 2005; Lodato et al., 2018).

Irreparable Structures: Definition and Classification

Long-lived irreparable structures are molecules, organelles, or tissues formed during early development that are not replaced throughout life. Their stability ensures specialized function, but the lack of regeneration makes them vulnerable to accumulating damage. These structures include:

Molecular Level:

- Lens crystallins—proteins ensuring lens transparency, synthesized during embryogenesis and not replaced later (Bloemendal et al., 2004).
- DNA in postmitotic cells (neurons, cardiomyocytes)—non-replicating, with repair mechanisms becoming less effective with age (Vermeij et al., 2016).

Organellar Level:

- Centrioles—cylindrical structures organizing the mitotic spindle; asymmetrically inherited in stem cells, accumulating age-related changes (Wang et al., 2021).
- Neuronal mitochondria—losing mitophagy capacity, leading to the accumulation of defective mtDNA (Sun et al., 2016).

Tissue Level:

- Tooth enamel—an acellular mineralized tissue incapable of regeneration (Selwitz et al., 2007).
- Central nervous system (CNS) neurons—do not regenerate axons after injury due to the expression of growth inhibitors (He & Jin, 2016).

These structures share a common principle: their longevity results from a trade-off between stability and functionality. For example, enamel mineralization protects teeth but prevents self-repair, while neuronal division cessation preserves neural networks necessary for memory but makes the brain vulnerable to trauma (Herculano-Houzel, 2014).

Entropy Accumulation as a Driving Force of Aging

According to the second law of thermodynamics, all systems tend toward increased entropy. In biology, this is

expressed as oxidative DNA damage, protein denaturation, and organelle dysfunction. The body combats entropy through self-repair systems—DNA repair, antioxidants, and cellular renewal. However, irreparable structures escape these mechanisms, becoming "hotspots" of accumulated damage:

- Oxidative stress: Reactive oxygen species (ROS) generated by mitochondria oxidize lens crystallins, leading to aggregation and cataracts (Truscott, 2005).
- Epigenetic changes: DNA methylation accumulation in postmitotic neurons disrupts gene expression related to synaptic plasticity (Xiong et al., 2020).
- Mechanical wear: Tooth enamel gradually erodes, exposing dentin and increasing sensitivity (Lussi et al., 2012).

The "garbage accumulation theory" suggests that aging accelerates due to cells' inability to remove damaged components (Terman & Brunk, 2006). Lipofuscin, a product of lipid and protein oxidation, accumulates in neuronal lysosomes, blocking autophagy and enhancing apoptosis (Höhn & Grune, 2013).

Compromises: Why Is Regeneration Impossible?

Across species, the ability to regenerate is often sacrificed for specialization. For instance:

- CNS neurons: The absence of mitosis prevents tumor formation risk but makes the nervous system vulnerable to injury (Frade & López-Sánchez, 2010).
- Lens: Loss of nuclei and organelles in lenticular cells minimizes light scattering but eliminates new protein synthesis (Bassnett et al., 2011).
- Centrioles: Their stability in stem cells ensures asymmetric division but promotes tissue aging through the inheritance of "old" centrioles (Nigg & Holland, 2018).

These trade-offs reflect a balance between immediate advantages (e.g., lens transparency) and long-term costs (e.g., cataract risk).

Clinical Relevance: From Molecular Damage to Disease

The accumulation of damage in irreparable structures underlies many age-related diseases:

- Cataracts: Lens opacity due to crystallin aggregation—a leading cause of blindness (Asbell et al., 2005).
- Alzheimer's disease: Accumulation of tau protein and β-amyloid in neurons is linked to nuclear pore and mitochondrial dysfunction (Scheltens et al., 2021).
- Heart failure: mtDNA mutations in cardiomyocytes impair energy metabolism (Brown et al., 2017).
- Dental caries and enamel erosion: Demineralization leads to irreversible tooth destruction (Pitts et al., 2017).

These conditions highlight the need for strategies to slow or reverse entropy accumulation.

Modern Approaches to Combating Entropy

- Senolytics: Drugs like fisetin and dasatinib selectively eliminate senescent cells, reducing the burden of "molecular debris" (Yousefzadeh et al., 2018).
- Gene therapy:

    - CRISPR/Cas9 correction of mutations in postmitotic neurons (Moreno et al., 2022).
    - Telomerase activation to extend stem cell lifespan (Jaskelioff et al., 2011).
- Biomimetic materials:
    - Hydroxyapatite nanoparticles mimicking enamel structure (Ruan et al., 2016).
    - Artificial chaperones stabilizing denatured proteins (Makley et al., 2015).

Understanding the interplay between irreparable structures and entropy paves the way for novel anti-aging interventions.

Modern Approaches to Combating Entropy

Senolytics: Compounds such as fisetin and dasatinib selectively eliminate senescent cells, thereby reducing the burden of accumulated "molecular debris," which is known to contribute to aging-related dysfunctions (Yousefzadeh et al., 2018).

Gene Therapy:

- CRISPR/Cas9-mediated correction of mutations in postmitotic neurons, aiming to restore genomic integrity and cellular function (Moreno et al., 2022).
- Telomerase activation as a strategy to prolong the lifespan and regenerative potential of stem cells, counteracting telomere attrition and cellular senescence (Jaskelioff et al., 2011).

Biomimetic Materials:

- Hydroxyapatite nanoparticles engineered to mimic the structural composition of enamel, offering potential applications in dental tissue regeneration (Ruan et al., 2016).
- Artificial chaperones designed to stabilize denatured proteins and prevent aggregation-related cellular stress (Makley et al., 2015).

Mitochondrial Replacement Therapy: Mitochondrial transplantation into oocytes has demonstrated potential in improving fertility by restoring cellular bioenergetics and reducing mitochondrial dysfunction (Fakih et al., 2021).

Centrioles: A Novel Target in Aging Research

Once regarded solely as microtubule-organizing centers, centrioles are now recognized as key regulators of cellular entropy. Their selective inheritance in stem cells plays a crucial role in tissue homeostasis but also poses a paradox: it contributes to the retention of damaged structures. Notable examples include:

- Disruption of Asymmetric Division: Aging centrioles in intestinal stem cells have been linked to impaired epithelial regeneration and reduced tissue repair capacity (Liang et al., 2020).
- Cancer Implications: Supernumerary centrioles contribute to chromosomal instability, a hallmark of tumorigenesis (Nigg & Holland, 2018).

Emerging therapeutic strategies include oxidative stress inhibitors (e.g., N-acetylcysteine) and gene-editing approaches targeting centriole-associated proteins (Zhong et al., 2022).

Objective of This Study

This article explores the role of long-lived, irreplaceable cellular structures in the aging process, integrating molecular, organellar, and tissue-level perspectives. The key areas of analysis include:

- Mechanisms of damage accumulation within these structures.
- Their association with age-related pathologies.
- Evolutionary constraints limiting regenerative capacity.
- Cutting-edge therapeutic strategies, spanning genetic engineering to biomimetic solutions.

By synthesizing insights from neuroscience, gerontology, and materials science, this review offers a multidisciplinary approach to understanding and potentially mitigating aging.

Long-Lived, Irreplaceable Molecules

Lens Crystallins

Crystallins are a specialized family of structural proteins that confer transparency and refractive properties to the eye's lens. These proteins are predominantly synthesized during early development and remain largely unrenewed throughout life (Bloemendal et al., 2004). Their exceptional longevity is vital for maintaining optical clarity; however, the absence of regeneration renders them susceptible to cumulative damage, a major factor in age-related cataract formation—the leading cause of blindness worldwide (Moreau & King, 2012).

Crystallins constitute up to 90% of the water-soluble proteins in the lens. In mammals, they are classified into three major families: α-, β-, and γ-crystallins. α-Crystallins function as molecular chaperones, preventing protein aggregation under stress conditions (Horwitz, 2003). β- and γ-Crystallins form a highly ordered structural network, maintaining transparency through high solubility and precise molecular spacing (Slingsby & Wistow, 2014).

With aging, crystallins undergo extensive post-translational modifications, including oxidation, deamidation, fragmentation, and glycation (Hains & Truscott, 2007). These alterations compromise solubility and promote aggregation. For instance, oxidation of methionine and cysteine residues in γ-crystallins triggers protein denaturation, while UV exposure accelerates photooxidation (Truscott, 2005). Accumulation of modified proteins leads to light scattering and cataract formation (Michael & Bron, 2011).

The avascular nature of the lens necessitates reliance on intrinsic antioxidant defenses (e.g., glutathione, ascorbate) and α-crystallin chaperone activity. However, with age, glutathione levels decline, and chaperones become increasingly engaged in counteracting damaged proteins, thereby losing their protective capacity (Kantorow et al., 2020). In vitro studies confirm that oxidized crystallins form protease-resistant aggregates (Sharma & Santhoshkumar, 2009).

Cataracts affect approximately 50% of individuals over the age of 80 (Asbell et al., 2005). Surgical lens replacement remains

the only effective treatment, underscoring the need for preventive strategies. Promising approaches involve the development of antioxidants and chaperone-mimetic molecules designed to stabilize crystallins and delay aggregation (Makley et al., 2015).

DNA in Postmitotic Cells

Postmitotic cells, such as neurons and cardiomyocytes, lose their ability to divide following terminal differentiation. Consequently, their DNA does not undergo replication, making repair mechanisms the sole defense against genomic damage. With age, the efficiency of these repair systems declines, leading to the accumulation of mutations linked to neurodegeneration and cellular senescence (Lodato et al., 2018).

Unlike proliferative cells, where replication errors can be corrected in subsequent cell cycles, postmitotic cells depend entirely on base excision repair (BER), nucleotide excision repair (NER), and homologous recombination mechanisms (Hoeijmakers, 2009). However, chronic exposure to oxidative stress and environmental insults overwhelms these repair pathways (Maynard et al., 2015).

Key contributors to DNA damage include reactive oxygen species (ROS) generated by mitochondria and exogenous factors such as UV radiation and chemical carcinogens. ROS induce base oxidation, strand breaks, and DNA-protein crosslinks (Halliwell, 2013). Neurons are particularly vulnerable due to their high metabolic demands and limited antioxidant defenses (Madabhushi et al., 2014).

Murine studies indicate that the activity of BER enzymes, such as OGG1, declines with age (López-Otín et al., 2013). The accumulation of oxidized bases, such as 8-oxoG, disrupts transcription and triggers apoptotic pathways (Lu et al., 2004). Additionally, age-related downregulation of repair genes like XRCC1 and PARP1 has been observed in neuronal populations (Fischer et al., 2016).

Somatic mutations in neurons are associated with neurodegenerative disorders, including Alzheimer's and Parkinson's disease (Jiang et al., 2017). In cardiomyocytes, accumulated DNA damage has been implicated in arrhythmias and heart failure (Oh et al., 2020). Potential therapeutic interventions include enhancing DNA repair enzyme activity (e.g., NAD+ boosters to stimulate PARP1) and employing mitochondrial-targeted antioxidants (Verdin, 2015).

Nuclei in Postmitotic Cells

The nuclei of neurons and other non-dividing cells do not undergo replication, making their components, such as nuclear pores and lamina, particularly susceptible to age-related damage (D’Angelo et al., 2009).

The nuclear lamina, which is composed of lamin proteins, provides mechanical stability and plays a crucial role in chromatin organization (Gruenbaum & Foisner, 2015). Nuclear pore complexes (NPCs) are responsible for regulating the transport of molecules between the cytoplasm and the nucleus. In neurons, NPCs contain proteins such as Nup107 and Nup133, which exhibit an extremely low turnover rate (Savas et al., 2012).

With aging, lamin proteins accumulate oxidative modifications and cross-linking events, leading to fragmentation of the nuclear envelope (Hernandez et al., 2010). Mutations in the LMNA gene, which encodes lamin A, are associated with progeria, a syndrome characterized by accelerated aging (Scaffidi & Misteli, 2006). In neurons, NPC dysfunction disrupts RNA and protein transport, contributing to neurodegenerative processes (Grima et al., 2017).

Compromised nuclear envelope integrity triggers stress response pathways, including p53-dependent apoptosis (Ivanov et al., 2013). In Alzheimer's disease, tau protein aggregates interfere with lamin-chromatin interactions, exacerbating transcriptional instability (Frost et al., 2014).

Pharmacological approaches such as farnesyltransferase inhibitors are being investigated for their potential to correct lamin defects in progeria (Capell et al., 2005). Additionally, antioxidant compounds are being explored as a means to slow down the oxidative degradation of nuclear proteins (Höhn et al., 2017).

Cilia in Retinal Photoreceptors

Photoreceptor cilia are highly specialized organelles responsible for converting light into neural signals. Their inability to regenerate after damage results in irreversible vision loss (Wheway et al., 2018).

These cilia possess an axoneme composed of microtubules in a 9+0 arrangement and contain intraflagellar transport (IFT) complexes that mediate protein trafficking (Pazour & Witman, 2003). While the outer segment of photoreceptors undergoes continuous renewal through the turnover of rhodopsin-containing disks, the basal segment of the cilium remains structurally stable (Insinna & Besharse, 2008).

Mutations in genes encoding ciliary proteins, such as RPGR and CEP290, impair rhodopsin transport and lead to retinal degenerative disorders such as retinitis pigmentosa (Hartong et al., 2006). Oxidative stress further accelerates axoneme degeneration, particularly in age-related macular degeneration (AMD) (Kaarniranta et al., 2020).

Photoreceptor ciliary loss is a key contributor to hereditary retinal dystrophies, including Stargardt disease (Molday et al., 2015). In AMD, lipofuscin accumulation in the retinal pigment epithelium (RPE) disrupts ciliary metabolism, exacerbating degeneration (Sparrow et al., 2012). Gene therapy approaches, such as voretigene neparvovec for RPE65 mutations, aim to restore ciliary function (Russell et al., 2017). Future therapies focus on CRISPR-mediated mutation correction and antioxidant strategies, such as lutein supplementation, to mitigate oxidative damage (Burnight et al., 2017).

Selective and Irreversible Inheritance of Centrioles

Unlike many cellular components that undergo limited renewal, centrioles are remarkable in their complete inability to regenerate. These cylindrical microtubule-based structures play a fundamental role in establishing the asymmetric molecular composition of mitotic poles and in ciliogenesis. In both postmitotic

and stem cells, centrioles remain unchanged throughout the cell's lifetime. Their selective inheritance during asymmetric cell divisions influences the fate of daughter cells and impacts tissue aging (Wang et al., 2021). New centrioles are inherited by daughter cells that commit to differentiation—cells destined for short-lived lineages or, in some cases, postmitotic fates.

Centrioles consist of nine triplet microtubules stabilized by proteins such as SAS-6 and CEP135. In non-dividing cells, they function as basal bodies for primary cilia, which regulate key signaling pathways, including Hedgehog and Wnt (Fu et al., 2015). Stem cells exhibit extraordinary centriole longevity, with some persisting for the entire lifespan of the organism (Bazzi & Anderson, 2014).

During asymmetric stem cell division (e.g., in neural and epithelial tissues), the "older" mother centrioles are selectively retained by the self-renewing stem cell, while the "younger" daughter centrioles are passed to the differentiating progeny (Pazour & Witman, 2003). This segregation is regulated by proteins such as POC1 and CEP120, which serve as markers of centriole age (Ye et al., 2021). Studies in Drosophila suggest that cells inheriting older centrioles exhibit greater stress resistance and slower aging (Rogers & Rogers, 2008).

Because centrioles do not undergo renewal, they accumulate oxidative damage and post-translational modifications over time. For instance, carbonylation of centrosomal proteins impairs microtubule assembly, potentially contributing to aneuploidy and age-related declines in tissue regeneration (Löhr et al., 2017). In neurons, defective centrioles are associated with primary cilia loss and disrupted signaling pathways, which are implicated in Alzheimer's disease (Guemez-Gamboa et al., 2014).

Centriole dysfunction is linked to progeria, neurodegeneration, and cancer. Mutations in centrosomal genes, such as PLK4 and CEP152, result in microcephaly and developmental abnormalities (Nigg & Holland, 2018). Over time, the accumulation of damaged centrioles in stem cells compromises their ability to undergo asymmetric division, leading to stem cell exhaustion (Liang et al., 2020) and a decline in proliferation rates.

Potential interventions focus on stabilizing centrioles through oxidative stress inhibitors (e.g., N-acetylcysteine) and modulating proteins that regulate centriole inheritance (Choi et al., 2020). Gene-editing technologies such as CRISPR/Cas9 are also being explored to correct defects in centrosomal components (Zhong et al., 2022). Given the profound impact of centrioles on aging and their role in cellular asymmetry, future approaches may involve de novo centriole synthesis in stem cells to restore division rates and maintain their regulatory influence over DNA, RNA, and protein activities. Notably, once centrioles fulfill their primary function of asymmetrically distributing molecular components during mitosis, they are either eliminated (e.g., in oocytes) or inactivated (e.g., in neurons). However, in stem cells—critical for tissue regeneration—centrioles are never eliminated or inactivated. Despite selective retention of older centrioles in self-renewing stem cells, these structures remain essential for sustaining the regenerative potential of tissues.

Oocytes in Women

Oocytes, which are the female gametes, originate during the embryonic stage and remain stored in the ovaries until reproductive maturity is reached. Due to their incapacity for renewal, these cells are highly susceptible to accumulating damage over time, ultimately leading to reduced fertility and an increased risk of aneuploidy (Titus et al., 2013).

The process of oogenesis initiates the formation of oocytes around the 20th week of intrauterine development. At this point, these cells enter meiotic prophase I and remain arrested in this state until puberty. A female is born with approximately 1 to 2 million oocytes, but by the time she reaches menopause, this number declines dramatically to around 1,000 (Wallace & Kelsey, 2010).

Prolonged dormancy of oocytes, which can last up to five decades, leads to the following detrimental consequences:

- Oxidative stress: Mitochondria in oocytes generate reactive oxygen species (ROS), which cause damage to mitochondrial DNA (mtDNA) and proteins, thereby impairing cellular function (May-Panloup et al., 2016).
- Epigenetic alterations: Changes in DNA methylation patterns and histone modifications disrupt gene expression, leading to functional decline (Xiong et al., 2020).
- Mitochondrial quality deterioration: A reduction in mtDNA copy number and dysfunction of the electron transport chain (ETC) results in decreased ATP production, which compromises cellular energy homeostasis (Van Blerkom, 2011).

With advancing age, several risks increase:

- Chromosomal abnormalities: Between 70% and 90% of embryos conceived by women older than 40 exhibit aneuploidy (Franasiak et al., 2014).
- Declining fertility: By the age of 35, the probability of conceiving naturally is reduced by 50% compared to younger women (Broekmans et al., 2007).
- Spontaneous miscarriages: The rate of pregnancy loss rises from 10% in women aged 20–30 years to nearly 50% by age 45 (Nybo Andersen et al., 2000).

Therapeutic Strategies

- Oocyte cryopreservation: Preserving oocytes at a younger age helps maintain fertility potential (Cobo et al., 2018).
- Mitochondrial replacement therapy: Transplantation of mitochondria from donor oocytes enhances metabolic efficiency and energy production (Fakih et al., 2021).
- Antioxidant supplementation: Coenzyme Q10 and melatonin have demonstrated efficacy in mitigating oxidative stress, thereby improving oocyte quality (Rudick et al., 2019).

Neurons in the Brain

Neurons within the central nervous system (CNS) are classified as post-mitotic cells, meaning they do not undergo division once differentiation is complete. Their axons and dendrites, in contrast to peripheral nerves, exhibit extremely limited regenerative

potential, rendering them highly vulnerable to injury, neurodegenerative diseases, and age-related deterioration (He & Jin, 2016).

Neurons are composed of a soma (cell body), dendrites, and a myelin-covered axon. In the CNS, axons are ensheathed by oligodendrocytes, which, unlike Schwann cells in the peripheral nervous system, secrete growth-inhibitory molecules such as Nogo-A, thereby actively preventing axonal regeneration (Schwab & Strittmatter, 2014). Additionally, the formation of a glial scar following trauma creates both physical and biochemical barriers that obstruct axonal repair (Bradbury & Burnside, 2019).

Barriers to Regeneration

- Expression of inhibitory molecules: Proteins such as Nogo, MAG, and OMgp interact with the NgR receptor on axons, activating the Rho-kinase pathway, which destabilizes the cytoskeleton and halts regrowth (Geoffroy & Zheng, 2014).
- Insufficient activation of regenerative pathways: Unlike peripheral neurons, CNS neurons exhibit minimal expression of pro-regenerative genes, such as GAP-43 and STAT3, even following injury (Tedeschi & Bradke, 2017).
- Energy deficits: Mitochondrial dysfunction in long axons results in ATP shortages, impairing the remodeling of membranes and the synthesis of essential proteins (Zheng et al., 2021).

Clinical Implications

- Neurodegenerative disorders: Conditions like Alzheimer's and Parkinson's disease are characterized by progressive neuronal loss, which the body cannot adequately compensate for (Hou et al., 2019).
- Spinal cord injuries: Damage to axons in the spinal cord leads to irreversible loss of motor and sensory function (Ahuja et al., 2017).
- Aging-related cognitive decline: The accumulation of tau protein and β-amyloid disrupts synaptic plasticity, exacerbating cognitive impairment (Scheltens et al., 2021).

Potential Therapeutic Approaches

- Inhibition of growth-inhibitory signaling: Antibodies targeting Nogo-A, such as Ozanezumab, have demonstrated axonal regeneration potential in preclinical models (Kucher et al., 2018).
- Enhancement of endogenous repair mechanisms: Administration of growth factors (BDNF, NT-3) and CRISPR-based gene activation (Lin28) have been explored as means to stimulate neuronal regeneration (Byrne et al., 2020).
- Cell therapy: Transplantation of induced pluripotent stem cells (iPSCs) and oligodendrocytes has shown promise in restoring myelin integrity and synaptic function (Assinck et al., 2017).

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Dental Enamel

Dental enamel is the hardest tissue in the human body, consisting of approximately 96% mineral content, primarily in the form of hydroxyapatite. It is acellular and lacks the ability to regenerate, rendering any structural damage irreversible without medical intervention (Selwitz et al., 2007).
Enamel formation is orchestrated by ameloblasts during the process of amelogenesis, which concludes before tooth eruption. Once enamel is fully formed, ameloblasts undergo programmed cell death, leaving the enamel without intrinsic mechanisms for self-repair (Simmer et al., 2010). Hydroxyapatite crystals within enamel are organized into prismatic structures, which enhance mechanical

strength but contribute to brittleness under uneven loading conditions (Beniash et al., 2019).

Causes of Enamel Degradation

- Caries: Bacteria, particularly Streptococcus mutans, metabolize sugars, producing acids that demineralize enamel (Pitts et al., 2017).
- Erosion: Dietary acids (from citrus fruits, carbonated beverages) and gastric acid (in cases of acid reflux) dissolve the outer enamel layer (Lussi et al., 2012).
- Mechanical wear: Bruxism and improper tooth brushing techniques contribute to microcracks and enamel thinning (Wetselaar et al., 2016).

Restorative Strategies

- Filling materials: Composite resins and amalgam are used to restore cavities but lack the ability to integrate seamlessly with natural enamel (Demarco et al., 2012).
- Veneers and crowns: Ceramic restorations reconstruct lost enamel structure but require substantial removal of existing tooth material (Peumans et al., 2000).
- Remineralization techniques: Nano-hydroxyapatite particles and bioactive peptides (such as P11-4) promote mineral deposition in early-stage enamel defects (Kirkham et al., 2020).

Discussion

The concept of irreparable structures within an organism presents a unique paradox: their longevity is critical for maintaining specialized functions, yet their inability to regenerate renders them vulnerable to age-related damage. However, the notion of "irreparability" is often relative, depending on the type of cells, organelles, and molecular context in which they exist.

The Relativity of Irreparability: Cellular and Evolutionary Context

The capacity for renewal varies even among structurally similar components. For example, mitochondria in skeletal muscle undergo partial replacement via mitophagy and biogenesis, processes activated by physical exercise through AMPK-dependent pathways (Lira et al., 2013). In contrast, mitochondrial turnover in neurons and cardiomyocytes is severely restricted due to the low activity of the PINK1/Parkin pathway, a limitation that is crucial for preserving long-term synaptic connections and contractile function (Stevens et al., 2015). On the other hand, centrioles exhibit absolute irreparability; attempts to artificially regenerate them in somatic cells lead to aneuploidy and uncontrolled proliferation, processes closely linked to oncogenesis (Nigg & Holland, 2018). Interestingly, during embryogenesis, centrioles are synthesized de novo following the initial cleavage divisions, highlighting an evolutionary trade-off between stability and plasticity (Wang et al., 2021). This phenomenon may be linked to the necessity of preventing the inheritance of damaged centrioles, aligning

with the "selfish organelle" hypothesis (Satir & Christensen, 2007).

Accumulation of Damage and Aging Theory: From Molecular Chaos to Systemic Collapse

Long-lived structures act as "reservoirs" of cellular stress, supporting the "garbage accumulation" theory (López-Otín et al., 2013). Several examples illustrate this concept:

- Lipofuscin accumulation in neuronal lysosomes impairs autophagy by binding to cathepsins, thereby inhibiting the degradation of damaged proteins and exacerbating oxidative stress, ultimately triggering apoptosis through caspase activation (Höhn & Grune, 2013).
- Denatured crystallins in the lens form amyloid-like aggregates, which scatter light and provoke inflammatory responses via NLRP3 inflammasome activation (Sharma et al., 2020).
- Damaged nuclear pores in neurons disrupt mRNA transport, leading to the accumulation of tau protein and β-amyloid, both key markers of Alzheimer's disease (Grima et al., 2017).

These processes are interconnected: dysfunction of one structure (e.g., mitochondria) accelerates damage in others (e.g., nuclear DNA), creating a vicious cycle of aging (Sun et al., 2016). For instance, mitochondrial ROS oxidize histones, impairing DNA repair by suppressing PARP1 activity (Fang et al., 2016).

Practical Implications and Therapeutic Strategies: Balancing Innovation and Risk

Understanding the mechanisms underlying irreparability opens avenues for:

Combating Age-Related Diseases

- Targeted lipofuscin clearance using senolytics (e.g., fisetin) selectively eliminates senescent cells, extending lifespan in model organisms by up to 30% (Yousefzadeh et al., 2018).
- CRISPR-based correction of mutations in postmitotic neurons using adeno-associated viruses (AAV) shows promise for treating Huntington's and Parkinson's diseases (Moreno et al., 2022).

Regenerative Medicine

- Biomimetic materials, such as hydroxyapatite nanoparticles functionalized with amelogenin peptides, induce enamel remineralization, restoring up to 80% of its original strength (Ruan et al., 2016).
- Mitochondrial transplantation via microinjection into oocytes enhances fertility in women experiencing age-related decline in egg quality, increasing implantation rates by 20% (Fakih et al., 2021).

However, interventions targeting irreparable systems require caution. For example, promoting axonal regeneration in the CNS through Nogo-A inhibition can lead to neuropathic pain due to abnormal growth of sensory fibers (Geoffroy & Zheng, 2014). Similarly, overexpression of chaperones

such as α-crystallin, while slowing cataract progression, may disrupt lens transparency by inducing excessively dense protein clustering (Makley et al., 2015).

Future Directions

Observing organisms with near-limitless regenerative capacity, such as planarians—whose cells containing centrioles do not divide—it becomes evident that species with dividing cells that possess centrioles have sacrificed regenerative potential in favor of specialization. Loss of mitotic activity in such species correlates with other evolutionary advantages. For instance, in neurons, this trade-off has facilitated the formation of stable neural networks essential for long-term memory but has also rendered the brain susceptible to injury (Herculano-Houzel, 2014). Similarly, enamel mineralization provides mechanical protection but precludes self-repair.

Promising research directions include:

- Development of "smart" biomaterials that mimic the hierarchical architecture of natural tissues (e.g., gradient hydrogels for axonal repair).
- Utilizing artificial intelligence to predict damage accumulation sites and tailor antioxidant therapies to individual needs.
- Investigating epigenetic clocks to assess the "age" of irreparable structures and determine optimal intervention points.

A particularly intriguing question is the accumulation of aged centrioles in stem cells.

Conclusion

Aging is a multifaceted process driven by the fundamental thermodynamic principle of entropy accumulation. In biological systems, entropy manifests as progressive molecular disorder caused by oxidative damage, DNA repair errors, and protein dysfunction. The organism continuously counteracts entropy by renewing cells and structures: hepatocytes regenerate every 150–200 days, skin epidermis every 2–4 weeks, and erythrocytes every 120 days (López-Otín et al., 2013). However, certain long-lived, irreparable molecules, organelles, and tissues serve as "entropy reservoirs," accelerating aging and predisposing individuals to age-related diseases.

Irreparable Structures as Entropy Accumulators

Molecular Level

- Lens crystallins, synthesized during embryonic development, remain unchanged throughout life. Their post-translational modifications (oxidation, glycation) promote aggregation, leading to cataracts—a major cause of blindness (Truscott, 2005).
- DNA in postmitotic cells (neurons, cardiomyocytes) accumulates mutations due to inefficient repair, correlating with neurodegeneration and heart failure (Lodato et al., 2018).

Organelle Level

- Mitochondria in neurons lose mitophagy capacity, accumulating defective mtDNA and generating

excessive reactive oxygen species (ROS), which trigger apoptosis (Sun et al., 2016).
- Centrioles in stem cells selectively inherit "old" maternal structures, disrupting asymmetric division and diminishing tissue regenerative potential (Wang et al., 2021).

Tissue Level

- Tooth enamel, devoid of cells, cannot regenerate, and its demineralization leads to irreversible structural damage (Selwitz et al., 2007).
- CNS neurons fail to regenerate axons following injury, attributed to the expression of growth inhibitors (Nogo-A) and the formation of glial scars (He & Jin, 2016).

Centrioles: The Principal "Conductors" of Cellular Entropy

Centrioles, unlike other cellular structures, occupy a unique position in the hierarchy of aging. They not only resist renewal but actively accumulate entropy, passing it on to subsequent generations of cells. In stem cells, "old" maternal centrioles are inherited by the cell maintaining stem cell properties, while "new" daughter centrioles are directed toward differentiating cells (Bazzi & Anderson, 2014). This mechanism, which is evolutionarily advantageous for maintaining the stem cell pool, has a downside:

Accumulation of Damage:

- Oxidation of centrosomal proteins (e.g., SAS-6) disrupts microtubule assembly, leading to chromosomal instability (Löhr et al., 2017).
- Aged centrioles lose the ability to form primary cilia, which blocks crucial signaling pathways (Hedgehog, Wnt) required for tissue regeneration (Satir & Christensen, 2007).

Impact on Gene Expression:

- Centrioles regulate the spatial organization of the nucleus through interactions with lamins and nuclear pores. Their dysfunction impairs mRNA transport and leads to the accumulation of damaged proteins (D'Angelo et al., 2009).
- In neurons, defective centrioles are associated with tau protein aggregation, a hallmark of Alzheimer's disease (Frost et al., 2014).

Association with Oncogenesis:

- Attempts at regenerating centrioles in somatic cells result in supernumerary centrioles, causing aneuploidy and uncontrolled cell division (Nigg & Holland, 2018).

Thus, centrioles become key accumulators of entropy, linking cellular aging to systemic dysfunction. Their stability, necessary for asymmetric division in stem cells, comes at the cost of progressively accumulating damage in tissues.

Strategies to Combat Entropy: From Theory to Practice

The body attempts to minimize entropy in irreparable structures through compensatory mechanisms:

- Autophagy: Removal of damaged organelles (e.g., mitochondria) through lysosomal degradation (Rubinsztein et al., 2015).
- Antioxidant Systems: Glutathione and superoxide dismutase neutralize

ROS, slowing protein and DNA oxidation (Sies et al., 2017).
- Molecular Chaperones: α-Crystallins prevent the aggregation of denatured proteins in the lens (Horwitz, 2003).

However, these systems are not flawless. For example, autophagy in neurons is suppressed with age due to the accumulation of lipofuscin (Höhn & Grune, 2013), and antioxidants are unable to fully neutralize mitochondrial ROS in cardiomyocytes (Brown et al., 2017).

Promising Therapeutic Approaches:

- Senolytics: Drugs (e.g., fisetin, dasatinib + quercetin) selectively eliminate senescent cells, reducing the burden of "molecular waste" (Yousefzadeh et al., 2018).
- Gene Therapy:
  - CRISPR/Cas9 correction of mutations in post-mitotic neurons (Moreno et al., 2022).
  - Activation of telomerase to extend the lifespan of stem cells (Jaskelioff et al., 2011).
- Biomimetic Materials:
  - Hydroxyapatite nanoparticles functionalized with amelogenin peptides restore tooth enamel (Ruan et al., 2016).
  - Artificial chaperones stabilize crystallins (Makley et al., 2015).
- Mitochondrial Replacement Therapy: Mitochondrial transplantation into oocytes improves fertility (Fakih et al., 2021).

Centrioles as a Target for Anti-Aging Therapies

Considering the role of centrioles in entropy accumulation, their stabilization or controlled replacement could become a breakthrough in combating aging:

- Oxidative Stress Inhibitors: N-Acetylcysteine slows the carbonylation of centrosomal proteins (Choi et al., 2020).
- Regulation of Asymmetric Division: Modulating proteins such as POC1 and CEP120 enhances the inheritance of "young" centrioles in stem cells (Ye et al., 2021).
- CRISPR Editing: Correcting mutations in centriole genes (PLK4, CEP152) prevents chromosomal abnormalities (Zhong et al., 2022).

However, any intervention requires caution. For example, excessive activation of centriole biogenesis can trigger cancer (Nigg & Holland, 2018).

Concluding Remarks

- Entropy as the Driving Force of Aging: Irreparable structures become "traps" for molecular chaos, disrupting tissue homeostasis.
- Centrioles as Key Players: Their selective inheritance in stem cells links cellular aging to systemic dysfunction.
- A Comprehensive Approach to Therapy: Combining senolytics, gene editing, and biomimetic materials can slow the accumulation of entropy. The strategy involves removing cells with old centrioles and replacing them with cells containing new centrioles. However, it must be ensured that new centrioles are functionally identical to

the old ones with respect to differentiation potential.

Future research should address the following questions:

- How can centrioles be "rejuvenated" without the risk of oncogenesis?
- Can regeneration be reactivated in strictly post-mitotic tissues (e.g., neurons, lens)?
- What role do epigenetic changes in irreparable structures play in aging?

Understanding these mechanisms will pave the way for radically extending healthspan, overcoming the limitations imposed by entropy.

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