Theory	Type	Core claim	Key evidence for	Key evidence against / limits	Evidence strength
Damage / error theories					
Free Radical / ROS Theory Harman, 1956	Damage	Reactive oxygen species from mitochondrial respiration accumulate and damage DNA, proteins, and lipids	Oxidative damage increases with age; antioxidant gene overexpression extends lifespan in some models; caloric restriction reduces ROS	Antioxidant supplementation fails to extend lifespan in humans or most animal studies; naked mole rats have high ROS yet exceptional longevity; most mt defects don't elevate ROS	Moderate — partially revised
Mitochondrial Free Radical Theory (MFRTA) Harman, 1972; refined by de Grey	Damage	mtDNA mutations amplified by mitochondrial free radicals create a vicious cycle of respiratory chain decline	mtDNA mutator mice age prematurely; mt dysfunction is universal in old tissues; strong mechanistic link to hallmarks 6 and 10	Amplification cycle not confirmed in vivo; mt mutator phenotype may reflect replication error not ROS; Kitazoe paper frames mt decline as entropic inevitability, not	Moderate-strong (mechanistic)

				damage-driven	
Somatic DNA Damage Theory Szilard, 1959; Vijg	Damage	Accumulation of unrepaired nuclear DNA damage drives cellular dysfunction and aging	Progeroid syndromes (Werner, Cockayne) are DNA repair defects; DNA damage increases with age; DNA repair capacity correlates with species lifespan	Yeast accumulate very few age-related mutations; damage accumulation rate seems too slow to be life-limiting vs. other processes	Moderate
SENS (Strategies for Engineered Negligible Senescence) Aubrey de Grey, ~2002	Damage	7 categories of cellular and molecular "damage" accumulate and could be repaired to reverse aging	Senolytics (targeting SENS category 2) now in human trials; some proof-of-concept in individual categories; unifying framework for translational research	Criticized as treating symptoms not causes; no integration across categories; damage-repair approach contested by Blagosklonny who argues damage is not life-limiting in normal aging	Mixed — varies by category

Telomere Attrition Theory Hayflick, 1961; Blackburn, Greider	Damage	Progressive telomere shortening limits cell replicative capacity, driving senescence and tissue aging	Telomerase knockout mice age faster; short telomeres predict mortality in humans; telomere length is a hallmark of aging (López-Otín 2023)	Post-mitotic tissues (neurons, cardiomyocytes) don't divide — telomeres irrelevant there; longer telomeres raise cancer risk (Haycock 2017 JAMA Oncol — our prior discussion); correlation ≠ causation	Strong for replicative tissues
Proteostasis / Protein Aggregate Theory Multiple; prominent in 2000s–2010s	Damage	Failure of protein quality control (chaperones, proteasome, autophagy) lets toxic aggregates accumulate	Ubiquitous in neurodegenerative disease (Aβ, α-syn, TDP-43); proteasome activity declines with age; restoring autophagy extends lifespan in model organisms	Aggregates may be consequence not cause; unclear whether systemic healthspan is limited by proteostasis vs. other drivers	Strong for neurodegeneration

Programmatic / quasi-programmed theories

Hyperfunction Theory Mikhail Blagosklonny, 2006–2024	Programmatic	Aging is driven by persistent, excessive activation of growth pathways (primarily mTOR) past their developmental purpose — a "quasi-program" never switched off	Rapamycin (mTOR inhibitor) extends lifespan in mice, flies, worms; improves immune function in elderly humans; predicts why caloric restriction works; unifies many hallmarks under one upstream driver	Most evidence is in model organisms; human RCT data on rapamycin as anti-aging drug is preliminary; debate with de Grey on whether damage is truly secondary	Strong and growing
Epigenetic Clock / Information Theory of Aging Horvath, 2013; Sinclair reframe ~2019	Programmatic	Aging results from loss of epigenetic information — DNA methylation patterns drift, disrupting gene regulation; Sinclair frames this as "corrupted software"	DNAm clocks predict biological age and mortality with high accuracy; partial epigenetic reprogramming (Yamanaka factors) reverses aging	Clocks predict age but causality unclear — methylation drift may be downstream of other drivers; Yamanaka reprogramming carries cancer risk;	Strong for biomarker; causal TBD

			markers in mice; epigenetic age is modifiable by lifestyle	human data limited	
Cellular Senescence / Inflammaging Hayflick, 1961; Campisi; Franceschi	Programmatic	Senescent "zombie" cells accumulate and drive systemic inflammation (SASP) that degrades tissue function across the organism	Clearance of p16+ senescent cells extends healthspan in mice; senolytics (dasatinib + quercetin, navitoclax) in early human trials; inflammaging predicts mortality; now a standalone hallmark (2023)	SASP has beneficial roles (wound healing, tumor suppression) — indiscriminate clearance has tradeoffs; human senolytic trial data still early	Very strong — leading translational target

Cellular Energy / Mitochondrial Density Theory Kitazoe & Toki, 2019–2026	Programmatic	Inevitable entropy-driven decline in mitochondrial density produces a gradual, exponential decline in cellular energy that is the common upstream driver of all aging hallmarks and imposes a biological lifespan limit (~105 Tc)	Fits Japanese mortality data precisely; mt density follows same exponential as msBMR; logistic model outperforms Gompertz/Kannisto on centenarian extrapolation; thermodynamically grounded	Cellular energy function is theoretically derived, not directly observed; limit of 105 depends on Japanese female data specifically; does not yet account for epigenetic or immunological mechanisms explicitly	Promising — limited independent replication
Evolutionary theories					
Antagonistic Pleiotropy George Williams, 1957	Evolutionary	Genes beneficial early in life (reproduction) are harmful later — natural selection cannot remove them because they confer early fitness advantage	Empirical support across many species; explains why aging is universal in reproducing organisms; mTOR fits as a molecular mechanism (beneficial in	Does not explain mechanisms; difficult to test directly; some observations (e.g. negligible senescence in lobsters, hydra) are hard to reconcile	Strong (evolutionary logic)

			development, harmful later)		
Disposable Soma Theory Thomas Kirkwood, 1977	Evolutionary	Organisms trade off somatic maintenance for reproduction — energy devoted to repair is energy not available for offspring, so maintenance is "good enough" but not perfect	Explains why caloric restriction extends lifespan (less energy to reproduction → more to maintenance); consistent with lifespan–reproduction tradeoffs in comparative biology	Challenged by Blagosklonny: if true, enhanced maintenance should fully prevent aging, but it doesn't; also doesn't explain post-reproductive aging in some species	Strong (comparative biology)
Emerging / frontier theories					
Developmental / Ontogenetic Theory João Pedro de Magalhães; Vladimir Dilman	Emerging	Aging is a continuation of developmental programs that simply never stop — like a house builder who keeps laying carpet after the house is finished	Shares predictive power with Hyperfunction Theory; explains why IIS/mTOR axis controls aging rate across species; complements Blagosklonny framework	Largely conceptual; hard to distinguish empirically from Hyperfunction Theory; doesn't fully explain post-mitotic tissue aging	Early — conceptual framework

Bioelectricity / Morphostasis Theory Léo Pio-Lopez & Michael Levin, 2023–2024	Emerging	Aging is a failure of bioelectrically-encoded morphostasis — cells lose the voltage-gradient "software" that coordinates tissue-level anatomical maintenance; drift in "morphospace" produces aging phenotypes	Ion channels implicated in multiple aging hallmarks; bioelectric manipulation induces regeneration in non-regenerative species; Vmem changes parallel senescence markers; links damage and programmatic theories	Very early; most evidence from model organisms (planaria, Xenopus); no human intervention data; therapeutic "morphoceuticals" are speculative	Very early — high theoretical interest
Extracellular Matrix (ECM) Aging Theory Statzer, Ewald et al., 2023	Emerging	Age-related stiffening and crosslinking of the ECM disrupts the mechanical and signaling environment of cells, driving senescence, stem cell exhaustion,	ECM stiffness increases with age in most tissues; AGE crosslinks accumulate; ECM composition regulates cell fate and identity; collagen crosslink	Proposed as 13th hallmark but not yet included; unclear if ECM changes are cause or downstream effect; human intervention data lacking	Growing — candidate hallmark

		and organ dysfunction	inhibition extends lifespan in C. elegans		
Two-Phase Aging Theory Rera, Zane et al., Frontiers in Aging 2024	Emerging	Aging consists of two distinct phases — a slow phase of gradual decline followed by a fast "end-of-life" transition — rather than a single continuous curve; onset of fast phase is the true mortality predictor	Demonstrated in Drosophila with intestinal permeability as the phase transition marker ("smurf" phenotype); two-phase pattern observed in worms and mammalian data; evolutionary model supports the timing	Human data limited; phase-transition biomarker not established for humans; mostly invertebrate model organism work to date	Early — invertebrate evidence