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MTOR-driven quasi-programmed aging as a disposable soma theory

Blind watchmaker vs. intelligent designer

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If life were created by intelligent design, we would indeed age from accumulation of molecular damage. Repair is costly and limited by energetic resources, and we would allocate resources rationally. But, albeit elegant, this design is fictional. Instead, nature blindly selects for short-term benefits of robust developmental growth. "Quasi-programmed" by the blind watchmaker, aging is a wasteful and aimless continuation of developmental growth, driven by nutrient-sensing, growth-promoting signaling pathways such as MTOR (mechanistic target of rapamycin). A continuous post-developmental activity of such gerogenic pathways leads to hyperfunctions (aging), loss of homeostasis, age-related diseases, non-random organ damage and death. This model is consistent with a view that (1) soma is disposable, (2) aging and menopause are not programmed and (3) accumulation of random molecular damage is not a cause of aging as we know it.

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Introduction

"Natural selection, the blind, unconscious, automatic process…has no purpose in mind. It has no mind and no mind's eye. It does not plan for the future. It has no vision, no foresight, no sight at all. If it can be said to play the role of watchmaker in nature, it is the blind watchmaker."[1] Richard Dawkins, *The Blind Watchmaker: Why the Evidence of Evolution Reveals a Universe without Design*.

The View from Intelligent Design

DNA, RNA, proteins, lipids, as well as structures containing these molecules can be damaged. Molecular damage constantly occurs. This must lead to aging. Molecular damage can be repaired. Yet, repair is energy-dependent and "expensive." And the organism, anyway, does not last forever, because it dies from extrinsic causes, such as predators, infections, starvation and accidents. Resource must be allocated: first to vital functions (such as brain respiration) to avoid immediate death, second to growth and reproduction and, third, to repair molecular damage to avoid "aging." And a truly intelligent designer will even calculate cost-effectiveness of anti-aging repair and design trade-off allocation between repair and reproduction to maximize reproductive success.

In the protected environment, where accidental causes of death are diminished, humans and laboratory/domesticated animals would die from aging (see Footnote 1).

1 Many advocates of programmed aging point out that some species of animals (especially, larger animals), live long enough in the wild to die from aging. Yes, some do (by the way, not Pacific Salmon, in which 98% individuals died before spawning (see ref. 14 for explanation); however, it does not mean that aging is either programmed or designed. It is still quasi-programmed. In natural "protected environments," when extrinsic death rate is temporarily low, nature selects for slow aging and aging tolerance (see aging tolerance in refs. 16 and 20), until most individuals live longer to die from extrinsic causes again. Therefore, aging in the wild may predominate in some species once in a while, because a natural "protected environment" may emerge occasionally. This does not argue for "programmed nature" of aging.

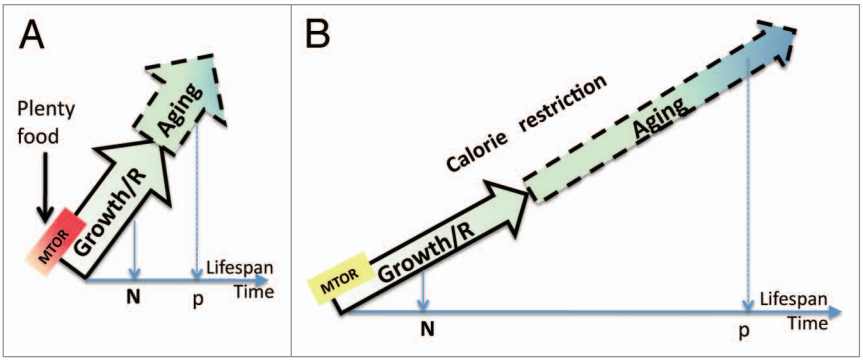

Figure 1. MTOR-driven quasi-programmed aging: plenty of food (overeating) vs. calorie restriction (famine). (**A**) Plenty of food: activation of the nutrient/MTOR and insulin/MTOR pathway. Calories are used for survival, growth and reproduction (R). Energy-dependent program of developmental growth continues as energy-dependent quasi-program of aging. N (natural), the typical lifespan in the wild; P (protected environment), the typical lifespan in the protected environment (humans, laboratory and domestic animals). In rare cases, protected environments can emerge naturally, especially among large animals. (**B**) Calorie restriction and famine: Especially during famine, calories/nutrients are used for immediate survival and only "leftovers" for program of developmental growth and reproduction (growth/R). N (natural), the typical lifespan in the wild during famine is short. There is no need to spend any calorie on anti-aging activities, no need to delay aging. P (protected environment), the typical lifespan in the protected environment (humans, laboratory and domestic animals). Lifespan is increased during calorie restriction under protected environment (ideally, no accidental death), exactly because resources are limited to drive energy-dependent quasi-programmed aging.

Blind Watchmaker

Unlike intelligent designer (ID), blind watchmaker (BW) cannot foresee aging. The BW is concerned with development, growth, reproduction and prevention of death from immediate causes: starvation, accidents, predators, weather, genetic and infectious diseases. Early in life, an animal must be strong and competitive. Activated by nutrients and growth factors, intracellular signaling networks including the MTOR (target of rapamycin) pathway stimulate growth,[2,3] muscle hypertrophy[4] and robustness.[5] Provided that nutrients (fuel) are readily available, MTOR is active or, metaphorically, "MoTOR" is running (**Fig. 1A**).

Because BW cannot design, she is extremely wasteful and messy. But even a small increase in fitness early in life justifies any waste. Furthermore, when development is finished, BW continues to spend energy on "twisted" growth or aging, which is purely harmful, energy-consuming and an unneeded process. But nature is blind. So how does growth convert into aging?

When developmental growth is completed, BW does not care to switch off growth programs driven by MTOR (and other related pathways). What for? Furthermore, MTOR is positively involved in reproduction. Also, the organism is likely to die from extrinsic causes anyway (**Fig. 1**). So nature is incapable of inhibiting MTOR just to prevent "future" aging. A hypothetical exception was discussed elsewhere.[6,7] One can calculate the cost-effect, but not because anti-aging efforts are limited by resources, but because MTOR is pleiotropic: useful early in life and harmful later. Later in life, MTOR causes cellular aging with inappropriate hyperfunction, an increased production of cytokines, resistance to signals, leading to loss of homeostasis, diseases of aging, organ damage and death, as recently discussed.[6]

BW is reluctant to constrain mTOR just in order to delay "aging." Survive right now is more important. The M(o)TOR is running, and the accelerator is stuck. By analogy, a car, running at 75 mph on the highway exits to a parking lot but continues to idle at full speed, as the accelerator is stuck. Importantly, even 50 mph will be too fast (see Footnote 2).

It is not BW, but starvation, scarce resources and stresses that de-activate the nutrient-sensing mTOR pathway, simply for mechanistic reasons not for the purpose of slowing aging. Starvation slows developmental growth, delays reproduction and aging (**Fig. 1A**), because aging is just driven by the same M(o)TOR, and this is why CR extends lifespan and overeating shortens it[14] (**Fig. 1**).

Both Models are Disposable Soma Theories (DST)

Soma is disposable by definition. Therefore, regardless of the mechanisms of aging, all models of aging are "disposable soma theories." For example, soma could be damaged by passive process, such as insufficient repair of molecular damage. As emphasized, "the aging process is caused by the gradual buildup of a huge number of individually tiny faults—some damage to a DNA strand here, a deranged protein molecule there and so on."[15] Or it can be damaged by an active process: myocardial infarction and stroke as a consequence of atherosclerosis, hypertension and thrombosis caused by MTOR-driven aging.[6,16]

It is misleading to call any one theory "simply" disposable soma theory (DST), implying that other theories are not DSTs.

DST One: Damage/Repair Theory

Known as "disposable soma theory (DST)," this theory postulates that: (1) accumulation of molecular damage causes aging, and (2) repair is costly and limited by resources.[15,17,18] Therefore, molecular damage is not repaired completely and eventually causes aging (in a protected environment). This is logical and intelligent. Actually, this is exactly what an intelligent designer would design. However, predictions of this model contradict observations, experiments and medical practice. If repair is limited by resources, the prediction must be the less resources, the shorter lifespan. And

2 In theory, either the MTOR activity or synthetic processes may be decreased later in life, but either not sufficiently or too late. For example, RNA/protein synthesis is decreased with aging in model organisms, yet its further inhibition prolongs lifespan,8-13 indicating insufficient natural decrease

vice versa, namely, over-nutrition would provide resources for repair and thereby extend lifespan. However, calorie restriction extends lifespan, whereas overeating shortens it.

To save the theory, it was suggested that during famine/starvation resources are allocated to anti-aging repair (**Fig. 1**). When starvation is over, then an organism would live a longer life, catching up with reproduction. This is paradoxical.[14,19] First, during famine, when the death rate is especially high, it would be sensible to allocate resources to vital functions and fitness, simply to prevent death from starvation and predators. Is it aging that always limits lifespan in the wild according to DST (and even despite famine when external death rate is exceptionally high). This contradicts the evolutionary theory. The DST (repair/damage) theory becomes internally inconsistent, leading to paradoxes as discussed.[14] It was even suggested that some harmful conditions such as menopause are programmed and have a purpose.[15] And would any rational designer extend life by inflicting damage (hormesis), indicating lack of design, as recently discussed?[20] And finally, deletion of numerous genes and processes not only improves an organism, but also extends lifespan.[21-36] What is a strange design? Should knockout of springs make clock-watches better? One must agree with Richard Dawkins that an intelligent designer (ID) has never existed. Aging, like life itself, have been shaped by blind watchmaker (BW).

DST Two: Hyperfunction Theory

In the BW scenario, an organism actively causes aging. BW uses energy to foster growth and then for its unneeded continuation, quasi-programmed aging. The long sequence of unforeseen events includes cellular hypertrophy, hyperplasia, hyperfunctions, loss of homeostasis, age-related diseases, organ damage and loss of functions.[37,38] At late stages, the process becomes MTOR-independent. Then malfunctions replace hyperfunctions. Since initial hyperfunctions are the most harmful, the model MTOR-driven quasi-programmed aging is becoming known as hyperfunction theory.[39]

Life without Food: Eating as Harmful Quasi-Programmed Hyperfunction

The most impressive example is lifespan extension by complete removal of food in *C. elegans*.[40] Whereas nutrients are essential for developmental growth, they are not needed in adult *C. elegans*, but even hurt them. Still, harmful eating continues. As was discussed in detail, nutrients, insulin and growth factors all activate TOR, driving growth and aging.[41] This explains why lack of food extends lifespan. This cannot be easily explained by any trade-offs between maintenance and reproduction.[40] The higher the MTOR activity, the faster the aging the way it is blindly "designed." An adult worm is actively seeking food, thus only accelerating its aging and death.

Gerogenic Conversion (Cellular Aging) and Organismal Aging

One of the most important features of hyperfunction theory is that organismal aging and age-related diseases can be easily explained by cellular aging on molecular mechanisms.[38,42,43] Cellular senescence is not just cell cycle arrest.[44] Senescence is not even necessarily cell cycle arrest (see Footnote 3). Cellular senescence develops when signal-transduction pathways, which drive metabolism and mass/size growth (nutrient-sensing, oncogenic, growth-promoting pathway, insulin/mitogen-sensing, gerogenic pathways), are activated, but the cell cycle is nevertheless blocked. Then the cell undergoes MTOR-driven geroconversion or conversion from quiescence/arrest to senescence.[45-59] Such gerogenic cells drive age-related diseases and organism aging.[38,60] Because rapamycin suppresses cellular geroconversion, the gerosuppressant rapamycin also suppresses age-related diseases and aging (See ref. 61 for review and references therein as well as most recent publications). Interestingly rapamycin can also affect not only geroconversion (physiological aging) but also so-called chronological aging in yeast[62] and cancer cells,[63] or in other words, acid-induced cell destruction.[63-65] Even more intriguingly, rapamycin can prevent replicative aging in certain conditions.[55,66-68] Most importantly, it can treat age-related diseases and[69-74] extend lifespan in old[75] and cancer-prone mice,[76] including mice lacking p53[77-80] and RB,[81] and slow down the aging process.[82,83]

Why Damage Cannot Cause Aging, as We Know It

Unlike pleotropic MTOR, which is useful early in life, random damage is harmful at any stage of life. Blind watchmaker is especially prone to overdo any necessary task for short-termed benefits. BW repairs it because it is harmful right now, not because BW is concerned with aging later. Broken bone needs to be repaired to save infant life. Molecular damage needs to be repaired too. Or consider progeria,[84-87] including Hutchinson-Gilford progeria (HGP) syndrome.[88] Infants and children with this syndrome would not be viable in the wild. They would die at a very young age. By a remarkable co-incidence, progeria in animals can be treated by rapamycin.[89-91]

So BW takes damage repair seriously: damage must be repaired regardless of aging, and this is why it is not a cause of aging. In addition, mutations initiate a sequence of events leading to cancer. Not despite but because of high mutation rate, cancer cells are robust (not weak), and multiple rounds of selection and proliferation non-randomly activate the MTOR pathway in cancer cells (for details, see ref. 92). Finally, BW may blindly repair some rare beneficial mutations too.

But still, damage accumulates. In theory, it will cause a new type of aging (at age of 130, for instance) if MTOR-driven quasi-programmed aging would

3 The difference between cell cycle arrest and senescence is unfortunately misunderstood. In the young organism, most cells are arrested but not senescent. They become senescent via gerogenic conversion. In cell culture, cell cycle arrest is a predisposition to senescence. Cell cycle arrest itself does not cause senescence but creates conditions for geroconversion from arrest to senescence.[44] MTOR generally causes growth and fosters proliferation, whereas rapamycin slows cell cycle progression and of course does not induce proliferation in the arrested cells.[44] What rapamycin and other inhibitors of MTOR do is suppress geroconversion (gerosuppression). Inhibitors of MTOR suppress some markers of senescent phenotype and preserve proliferative/regenerative (PP) potential, which is convenient to measure senescence. The potential to proliferate is not proliferation. This is the potential of normal young cell.

not terminate life first. By analogy, when in the past people died young from starvation, infections and accidents, then atherosclerosis could not kill them. Some age-related diseases were almost unknown until recently.

Quasi-Program is Not a Program

The evolutionary theory explains that aging cannot be programmed. Still the notion that aging is programmed persists and was even "re-invented." In my mind, the reason why theories of programmed aging are still "alive" is that aging is so program-like. Human age-related diseases and menopause have distinct molecular, cellular and systemic mechanisms, which are not random at all. How can random damage drive these processes that are so development-like? Even non-programmed random molecular damage theories accept that menopause and death of Pacific salmon are programmed. But, like aging itself, they are not: they are quasi-programmed.

A quasi-program looks like as a program, but it is not. It is a continuation of some useful developmental program. It is a by-product. Unlike an actual program it has no purpose, nor plan. By giving a new application to the Dawkins words, I have the courage to write that, as the blind continuation of developmental growth, a quasi-program of aging "has no purpose in mind. It has no mind and no mind's eye. It does not plan for the future. It has no vision, no foresight, no sight at all."[1]

Amazingly, logical thinking could create non-programmed "damage/repair" theories on one hand, and "programmed aging" theories on the other hand. In contrast, blind watchmaker may unsuspectingly create only quasi-programmed aging. Of course, "DST-one" was not intended as a design theory, but in contrast, like "DST-two," it was inspired by Darwinian theory of natural selection. But at the end, one may characterize DST-one as a flawed application of BW thinking that, inadvertently, has the character of intelligent invention when viewed through the lens of hyperfunction theory (DST-two).

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