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Solving Puzzles of Aging: From Disposable Soma to Signal-Transduction Pathways

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Abstract—Aging is believed to be caused by accumulation of unrepaired damage. The repair is believed to be limited by energetic resources. A testable prediction is: the less resources (calorie restriction), the shorter lifespan. In contrast, calorie restriction extends life span. To explain the conflicting result, paradoxical "allocation of resources" was proposed, thus creating the "odd science of aging." However, evidence emerges that aging is not driven by damage but instead is driven by nutrient-activated signaling pathways such as TOR (target of rapamycin). This immediately explains how calorie restriction extends life span and solves all "odd" puzzles of aging. Here I suggest that aging is neither random damage nor a program but instead is a quasi-program (a harmful continuation of valuable developmental programs). It is a genetic process that can be slowed down pharmacologically. And several drugs that directly or indirectly inhibit TOR are available for clinical use.

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INTRODUCTION

A provocative title announced that "Caloric restriction does not enhance longevity in all species and is unlikely to do so in humans" [1].

Calorie restriction (CR) increases both median and maximal lifespan in diverse species from unicellular yeast to large mammals [2–7]. CR not only extends life span but also delays diseases of aging. For example, CR prevents cancer in rodents [8–12]. And vice versa, unrestricted eating (*ad libitum*) shortens life span in almost all species. Why should humans be an exception? In fact, they are not. Overwhelming evidence indicates that unrestricted food consumption or eating as much as one enjoys (*ad libitum*) leads to obesity, which shortens human life. In contrast, reduction of body weight decreases the risk of developing all diseases of aging from heart disease to dementia and cancer [13, 14]. Furthermore, CR delays age-related diseases in non-obese humans [6, 15–18].

Yet, as advised by Kirkwood, "eat what you enjoy – to do otherwise might make you live longer, but for what purpose? – but train yourself to eat fewer calories, if you can. I find this hard, because I like food enormously" [19].

Allocation of Resources

Why does the topic of CR remain controversial? One explanation is that the anti-aging effect of CR rules out classic theories of aging. According to classic gerontology, aging is a functional decline due to accumulation of molecular damage. Still, molecular damage can be repaired. But repair is energetically costly. In somatic cells, there is no need to repair damage completely. There are many other tasks that require energy [20]. For example, mice die from starvation, infections, predators and freezing temperatures. Energetic resources are limited. Wild mice allocate resources to increase subcutaneous fat and heat production rather than to repair completely molecular damage. Unrepaired molecular damage accumulates. Thus, the insufficiency of resources (nutrients) causes aging. This predicts that abundant nutrients must slow aging down. And vice versa, calorie restriction (CR) must shorten lifespan.

In contrast, calorie restriction (CR) extends life span in a variety of species, including yeast, worms, flies, fish, mice, rats and primates [2–5, 21].

To solve the CR paradox, it was suggested that food shortage improves molecular repair. In other words, the less total resources, the more resources for

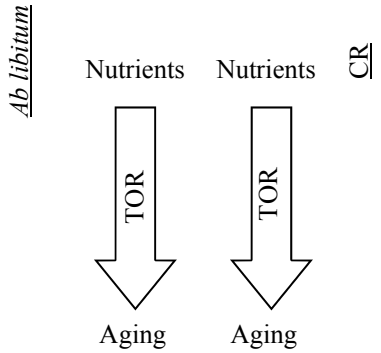

Fig. 1. Calorie restriction and aging. Nutrients activate the nutrient-sensing TOR (target of rapamycin) pathway, which in turn drives aging.

repair. This slows aging and allows the organism to reproduce later, when the famine is over. Delayed aging represents "a strategy to cope with periods of famine" [22]. In other words, survival during famine in the wild is limited by aging. This is odd [20]. A sensible biological strategy during famine should be to shut down anti-aging repair and to allocate all resources for immediate survival (for both sexes) and reproduction (for males). CR extends life span in both males and females, also contradicting the allocation hypothesis.

The allocation hypothesis leads to odd paradoxes. According to evolutionary theory (as pointed out by Kirkwood himself), inhibition of aging should not increase lifespan in the wild, because most animals die from external causes (such as starvation during famine) before they become old. The allocation hypothesis, in contrast, suggests that lifespan in the wild is limited by aging. Second, if organisms can inhibit aging during food shortages, then they purposely choose not to do so in normal conditions. And this implies a program for aging. And here is a new paradox. The allocation resources model was proposed exactly in order to argue that aging is not programmed. Instead the hypothesis predicts programmed aging.

Ideological Gerontology

Kirkwood named his model "disposable soma theory." [19] Yet, all theories of aging are "disposable soma theories." Soma is disposable by definition. Non-disposable soma is the germ line. Once August Weismann had divided life into perishable soma and immortal germ line, he introduced disposable soma theory. As Weismann wrote in 1889, "the perishable and vulnerable nature of the soma was the reason why nature made no effort to endow this part of the individual with a life of unlimited length" (see [23]). Any theory of aging (including TOR-driven aging) is a disposable soma theory. Misleadingly named as disposable soma theory, the allocation theory thus ironically has become dominant in gerontology. But the allocation theory contradicts observations. Thus gerontology has become a system of beliefs or ideology. The beliefs are: (1) aging is caused by accumulation of damage, (2) damage caused by life-long production of unwanted ROS, (3) repair is limited by resources, but (4) less resources, more repair, (5) aging cannot be programmed but reproductive aging (menopause) is programmed, (6) aging can be without diseases of aging, (7) disease are treatable but aging is not.

As for any beliefs, evidence is not needed. In some studies, increased ROS correlated with extended life span. This contradicts the dogma. Then it was suggested that increased ROS increases resistance to ROS, thus extending life span [24–26]. In other words, even contradictory data support the ideology. According to ideological gerontology, molecular damage stimulates repair mechanisms, which is turn prolong life span. Similarly, Baron Munchausen escaped from a swamp by pulling himself up by his own hair. If damage prolongs life span, then damage simply cannot be a cause of aging.

Let us consider the crucial belief: aging is caused by accumulation of damage. It looks like self-evident. Yet, this belief is not based on any evidence (see for ref. [27]). Do *C. elegans*, who live 20 days, die from accumulation of molecular damage? It does not [28–30]. To avoid misunderstanding, we need to emphasize that molecular damage may accumulate over lifetime. Yes, this accumulation must cause death eventually. But the point is: there is another process that kills the organism first. This process is active, program-like (quasi-programmed) and energy-dependent. And by the way, this immediately predicts that CR must extend life span (Fig. 1).

Beliefs do not need to be logical. It was suggested that menopause is beneficial [31–33]. According to a "grandmother hypothesis," post-reproductive women help their daughters to raise grandchildren. But what is a biological sense to stop reproduction, if a woman has no grandchildren living together with her? Also, mice undergo ovarian changes analogous to menopause in humans [34, 35]. Do mice raise grandchildren? Furthermore, "grandmother" hypothesis contradicts to other aspects of the same theory. If aging cannot be

programmed, why then reproductive aging can be programmed. Or why may aging be programmed in Pacific Salmon but not in humans? As stated by Kirkwood, "for most species, other than those like Pacific Salmon where death coincides directly with the end of a once-only reproductive cycle, there is scant evidence that senescence contributes significantly to mortality in the wild" [36] and, as continued by Austad, "aging, except in exceptional cases such as the rapid decay and death of Pacific salmon, is not design but decay" [37]. In particular, it was suggested that Pacific Salmon die in order to increase food supply for their offspring. If programmed aging is possible in Pacific Salmon, then programmed aging cannot be ruled out in other species.

May Aging be Programmed?

Aging looks like a program. Definitely, it is a genetic process. Aging can be delayed by genetic, caloric and pharmacological means. There are several examples. The nematode *Strongyloides ratti* live 5 days [38], whereas humans live 100 years. In *C elegans*, inactivation of PI-3K extends medium and maximal lifespan almost 10-fold [39].

Age-related conditions and diseases are clock-like. In women, irregular menstrual cycles with infertility will appear before menopause, whereas the propensity to bone fractures will arise after menopause. This is not random. There must be a program. But here is a problem. To be selected during evolution, a program must be useful. It was suggested that aging may accelerate evolution. For example, some favorable traits can be easier recognized in aging animals. Also, it was suggested that the population can benefit from the death of individuals [40–43]. This may (or may not) be correct in particular situations. Still the aging process is universal. How could such a harmful program as aging be so universal? Therefore, although aging is a non-random, genetic process, it might be easier to believe that aging is a random accumulation of damage.

TOR-Driven Quasi-Programmed Aging

But random damage is not a proper alternative to programmed aging. The proper alternative is quasi-programmed aging. ("Quasi-" means "as if, resembling").

Consider an analogy. After preparing a dinner (a program), you forgot to switch off heat and left a pot with boiling water on a red-hot stove. All water was boiled out and the pot was destroyed. There is no program for destroying a pot. You just neglected to switch off "a program" after its completion. Similarly, aging may be quasi-programmed. A quasi-program is an aimless continuation of a useful program that was not switched off upon its completion. Unlike programs, quasi-programs have no purpose. Like programs, quasi-programs are genetic, can be switched off genetically and pharmacologically. A quasi-program for aging is driven by antagonistic pleiotropic genes, which are beneficial early in life on the cost of aging later in life. As recently reviewed, many genes that control aging constitute the TOR (Target of Rapamycin) intracellular signaling pathway [44, 45]. The nutrient-fueled TOR (target of rapamycin) pathway drives developmental growth. In post-development, "red-hot" TOR drives aging.

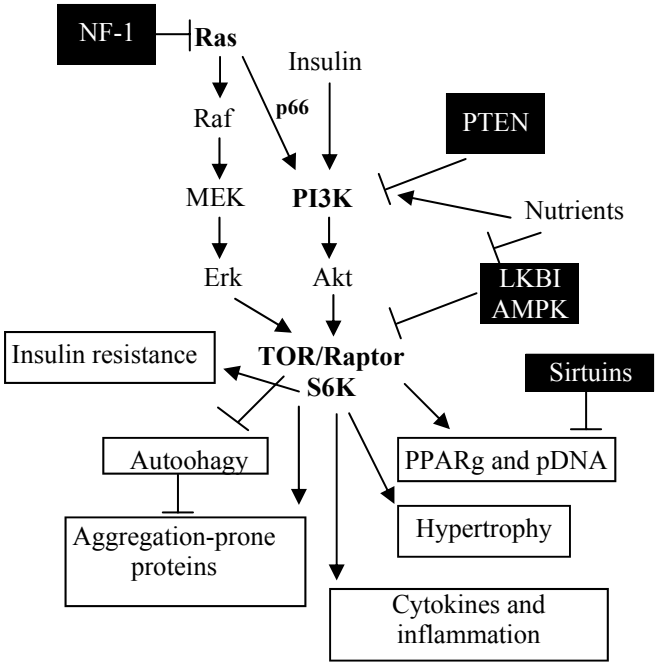

Fig. 2. The mTOR pathway. All genes, whose mutations affect life span (from yeast to mammals), can be arranged into the TOR pathway. Genes for longevity, whose inactivation shortens lifespan, are shown on the black background. Genes for aging, whose inactivation extends lifespan, are shown in bold. Like the Mendeleev periodic table had predicted new chemical elements, the aging pathway predicts longevity and aging genes, depending on whether they activate or antagonize TOR. Thus, Raf, MEK, ERK and Akt are likely to be genes for aging.

The TOR pathway is conserved in diverse organisms from plants to humans. In response to nutrients, hormones, IGF-1, insulin and other stimuli, TOR promotes cell (mass) growth (Fig. 2).

TOR is absolutely essential during embryonic development [46, 47]. In post-development, TOR is involved in aging and age-related diseases such as atherosclerosis, neurodegeneration, cancer, metabolic syndrome [44, 48]. Partial inactivation of the TOR pathway prolongs life span in yeast, worms, flies and mice [49–52].

The TOR pathway is essential for developmental growth. Once developmental growth is finished, overactivation of the TOR pathway becomes harmful. In other words, TOR-driven developmental program becomes a quasi-program for aging [44].

The stronger the force that drives growth, the faster the aging. For example, *C. elegans* grow during 3 days from the egg to an adult worm. This intensive growth-promoting force kills the worm fast (2–3 weeks), when actual growth ceased and is transformed into aging. Lack of nutrients or inhibition of the TOR pathway decreases the growth-promoting force and slows aging.

Thus, TOR-driven developmental program and TOR-driven quasi-program for aging may be a clear-cut example for the antagonistic pleiotropy theory. In *C. elegans*, deactivation of the PI-3K/TOR pathway extends lifespan. On the other hand, this deactivation causes a prolonged developmental arrest [39, 53]. Dwarf mice with low IGF-1 levels, have reduced body size, delayed puberty and extended lifespan [54, 55]. Inactivation of genes for aging has trade-off early in life. Unlike genetic knockout, inhibition of TOR with rapamycin could be started later in life (when TOR is harmful) without any trade-off early in life.

The Imprecision of Quasi-Programs

A quasi-program is not very precise because it is an unguided continuation of the developmental program. This is exactly in agreement with puzzling observations by Kirkwood: "if genes program aging, they do so only very loosely." This is in sharp contrast to the developmental process, which is so precisely regulated [20]. In fact, "loose" regulation is exactly what is expected from a quasi-program. Still the quasi-program is precise enough to cause the same age-related diseases in most mammals. Yet the quasi-program is not precise enough to cause these diseases synchronically in all individuals. Since aging is not a program, diseases are also variable in time of their onset, determining a variable life span. The later in life, the more variable. For example, presbiopia and menopause occur early in life and therefore are universal. Macular degeneration and Alzheimer's (later in life) are variable in onset: many people die from other causes without living long enough to develop these diseases.

Program *Versus* Quasi-Program

Quasi-program for aging has no purpose. This is the only one difference between programmed and quasi-programmed aging. For all practical applications, they are identical. In principle, some aging processes can be beneficial to grandchildren and even to an individual itself. But even then, this is simply co-incidental not intentional. Let us consider a hypothetical example. Gray hair might provide a selective advantage to ancient humans who migrated to the snowy North Europe. But still age-related gray hair are not programmed for that purpose. Instead evolution would select for blond hair in young individuals, who nevertheless become gray with age. Gray hair are observed in many aging mammals. Menopause in women is quasi-programmed too. It is a continuation of the same program that initially established the menstrual cycle [56]. Menopause is harmful. Menopause is not only reproductive death but also accelerates atherosclerosis, osteoporosis and cancer [57]. But it is a continuation of the program that started menses in the puberty.

What about Pacific Salmon? It is believed that Pacific Salmon die shortly after their first and only reproductive episode (spawning). If that were true, then a number of this would exponentially increase 2000 times every spawning. In reality, Pacific Salmon almost invariably die before spawning and only a few individuals survive until after reproduction (see analysis in [58, 59]). The only difference between Pacific Salmon and other animals is that Salmon reproduce very late in life. By that time, 99.8% of individuals die (from external causes) without reproduction. Both death of Salmon after spawning and death of laboratory animals are quasi-programmed.

Why CR Prolongs Lifespan: De-Activation of TOR

Calorie restriction (CR) de-activates the nutrient-sensing TOR pathway (Fig. 1). It was shown in yeast, flies and worms that CR inhibits aging by inhibiting TOR [49–51, 60–62]. In mammals, nutrients activate TOR and also cause insulin-resistance [63–69]. So, CR de-activates TOR (Fig. 1).

Cellular Aging

TOR drives growth and aging. When TOR cannot drive growth, it drives aging [70]. And aging is a

continuation of growth. In proliferating cells, TOR stimulates cellular mass growth, which is balanced by cell divisions. But when the cell cycle is blocked, TOR stimulates growth in size, activating compensatory events. This leads to senescence. In non-dividing cells, TOR should be de-activated to avoid senescence. In quiescent (resting) cells, the cell cycle is blocked and TOR is switched off. In contrast, if the cell cycle is blocked but TOR stimulates growth, they become senescence. It was shown that deactivation of TOR by rapamycin partially prevented cellular senescence. In summary, TOR drives cellular (mass) growth. But when the cell cycle is blocked, TOR drives cellular senescence [71].

Consider the sink analogy: a cell (a sink), TOR-driven growth (water coming into the sink from facets) and cell divisions (water leaving the sink via the hole). This is a normal condition in proliferating cells. Consider the cell cycle is blocked (the sink is plugged). When the sink is plugged and water is still coming from faucets, then this causes overflow. In order to prevent overflow, either the plug should be removed or water should be turned off. And continuous water flow into the plugged sink is analogous to cell senescence. What is most important in this analogy is that flood does not damage the sink itself. It damages distant objects: a TV set in the living room, books in the apartment below, for example. Similarly, cell senescence may affect distant organs and cause damage of the most vulnerable structures and functions.

From Cellular Senescence to Organismal Aging

How does inappropriate activation of cellular signaling pathways (such as TOR) cause aging? It does not cause aging. It *is* aging. The organ damage is secondary. Aging does not necessarily hurt the aging cell itself. It may hurt other cells, organs or the organism as a whole. For example, insulin resistance in muscle, fat and liver can (via a sequence of events) lead to renal failure, blindness and foot gangrene. As another example, TOR-induced hyper-function of osteoclasts can lead to broken hip and death due to pulmonary complications. Overactivated senescent stroma can promote breast cancer growth, which then damage the liver by metastases. Overactivation of arterial smooth muscle cells and blood platelets can contribute to stroke and brain damage. Hyper-activated TOR does not need to cause molecular damage in order to kill the organism.

Finally, hyper-stimulation of TOR not only causes cellular hyper-function, it also causes resistance to stimuli. For example, by feedback loop, activation of mTOR/S6K causes resistance to insulin and growth factors [63, 68, 72–76]. And the irresponsiveness to signals is one of hallmarks of aging cells. In their combination, cellular hyper-function and signal-resistance can cause organ failure and organismal damage, thus linking cellular senescence to organismal aging and death.

Rapamycin (Sirolimus, *Rapamune*)

Nephrologists are familiar with Sirolimus, a clinical drug that prevents rejection of transplanted organs. Yet, they perhaps are not familiar with genetic pathways that regulate longevity of *C. elegans*, for instance. And this pathway contains TOR (target of rapamycin). And rapamycin is known in the clinic as Sirolimus. Only by bringing together these different fields, we can conclude that a potential anti-aging drug is clinically available [77].

Rapamycin, an inhibitor of TOR, is an antifungal antibiotic produced by soil bacteria that inhibits yeast growth but extends life span of aging yeast. Given that TOR is involved in aging in diverse species, its inhibitor must be an anti-aging drug [45]. In fact, rapamycin slows down aging in yeast [51]. Why would bacteria produce an anti-aging drug? Nature has created a "drug against aging," exactly because its target is pleiotropic. This anti-aging drug is intended to hurt yeast earlier in life. By producing rapamycin, bacteria block yeast growth. The anti-growth effect hurts yeast, whereas the anti-aging effect of rapamycin is not important in the wild.

TOR is a potential target for therapeutic intervention. The TOR inhibitor rapamycin (Sirolimus) is a drug approved for clinical use [45]. Rapamycin has pre-clinical indications for therapy of age-related diseases from cancer to age-related macular degeneration [44, 78, 79].

Rapamycin and ROS

ROS and oxygen activate TOR [80, 81]. By activating TOR, ROS (in theory) may accelerate aging. And vice versa, mildly increased systemic TOR-S6K signaling sensitizes the whole organism to oxidative stress [82]. In turn, activation of the PI-3K/TOR pathway increases production of ROS, whereas inhibition of TOR decreases ROS levels [83, 84]. The TOR pathway regulates mitochondrial oxygen

consumption and oxidative capacity [85]. As discussed, over-activated TOR causes cellular hyper-functions [44]. The normal function of phagocytes is to produce ROS to attack microbes. Then the hyper-function of phagocytes is over-production of ROS without the presence of infection. A hyper-function of neutrophils to produce oxidative bursts contributes to rheumatoid arthritis and osteoarthritis, two common diseases of aging. Noteworthy, rapamycin decreased oxidative burst activity of neutrophils in humans [86].

SkQ, a mitoxondria-directed anti-oxidant, increased tolerance to diseases and increased median life span [87-89]. The effect on the maximal lifespan was less dramatic. Given a positive feedback loops between TOR and ROS, one may suggest to combine SkQ and rapamycin in order to maximally extend healthy lifespan.

Conclusion and Further Reading

There are many topics to discuss in detail. How unnecessary activation of mTOR causes cellular senescence. How cellular over-activation causes organ damage. How ever-increasing resistance to hormones starts menses in puberty and causes menopause later. How TOR activation in the liver and the fat tissue cells leads to blindness and renal failure.

However, these topics are beyond the scope of this brief article. There are several related recent publications on cellular senescence [70, 90]. There are several reviews on organismal aging and age-related diseases [27, 78, 91]. Some other reviews are still "fighting" their way to the readers. These reviews discuss the relationship between aging and damage, the path from cellular over-activation to organismal death, the link between cellular and organismal aging and age-related diseases, pleiotropic antagonistic genes, quasi-programs, mechanisms of the anti-aging effect of calorie restriction, mechanisms of diabetic complications and why these complications may precede the onset of diabetes itself. These manuscripts discuss insulin resistance and diabetic retinopathy, menopause and age-related diseases, suggesting new ways (if correct) to prevent blindness, foot amputations, strokes and hip fractures. Publication of each review is very time consuming. There are gaps between topics published so far. The theory remains fragmented. Therefore, these unpublished and published papers will be collected as chapters to constitute a single book, covering all fields from cellular senescence and mechanisms of aging to prevention and therapy of age-related diseases. A preliminary title is the *Origin of Aging*. I hope to refer readers to this book soon.

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