Cell Cycle

ISSN: 1538-4101 (Print) 1551-4005 (Online) Journal homepage: http://www.tandfonline.com/loi/kccy20

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To cite this article: Mikhail V Blagosklonny (2009) TOR-driven aging: Speeding car without brakes, Cell Cycle, 8:24, 4055-4059, DOI: 10.4161/cc.8.24.10310

To link to this article: http://dx.doi.org/10.4161/cc.8.24.10310

Published online: 15 Dec 2009.

Cell Cycle 8:24, 4055-4059; December 15, 2009; © 2009 Landes Bioscience

TOR-driven aging

Speeding car without brakes

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This article discusses that the traditional analogy of an aging organism with a rusting (albeit self-repairing) car is misleading. The true analogy is a speeding car that enters a low-speed zone and damages itself because it does not and cannot slow down. For such a car without brakes (and actually without a driver), aging from rusting never occurs. Using simple analogies (although turning gerontology upside down), this article discusses the origin of aging, how overactivation of the mTOR (Target of Rapamycin) pathway causes aging, why aging causes damage (organ damage) not damage causes aging, the link between aging and age-related diseases, slow aging versus aging tolerance and suppression of aging with rapamycin.

Key words: senescence, aging, mTOR, TOR, rapamycin

Submitted: 10/07/09

Accepted: 10/09/09

Previously published online: www.landesbioscience.com/journals/cc/article/10310

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Classic Analogy: Rusting Car and its Maintenance

Aging may look like decline, deterioration and loss of functions due to accumulation of molecular damage. Aging is often compared with "rusting" of living beings by free radicals. As the 'rusting car' analogy suggests, longevity of a car depends on its maintenance and repair. Sooner or later, all systems deteriorate and maintenance becomes too costly. It may be cheaper to dispose of an old car and to buy a new car. This is called disposable soma theory.[1] Yet, all and any theories of aging are "disposable soma theories," because soma is disposable by definition. Non-disposable soma is the germ line. Ironically, the car maintenance analogy is incorrect because, cars are not truly disposable (are not disposed of after the first ride). Unlike cars, living beings do not survive long enough to die from "rusting" (accumulation of molecular damage). According to the TOR-driven aging model,[2] living beings are truly disposable and are designed for a single ride. Our life is an (on average) 80-year-long ride in a car without brakes.

New Analogy: Car Without Brakes

According to alternative analogy, a powerful car is moving at the highest speed on a highway (youth). Then it enters a 20 mph-speed-limit road (adulthood) and yet continues to run at the highest speed. At first (and perhaps for a long time), there are no obvious problems despite high pressure on all systems. The car continues to run in the same direction regardless of turns of the road. Finally it damages itself, decelerates and stops after a final crash ("dead"). An observer may conclude that it is deceleration that causes 'death' of the car. Yet, the real cause is that the car did not slow down, when it entered the 20-mph road (adulthood). Perhaps the car has no brakes. Similarly, organisms do not slow in post-development. And the same force that initially drives developmental growth then causes aging and age-related diseases.[2-4]

Why Living Organisms Do Not have Breaks

In the wild, organisms do not live long enough to experience aging (**Fig. 1**). Therefore, they do not need "brakes." Most animals die from external causes such as predators, lack of nutrients, infections, before they even reach "a 20-mph

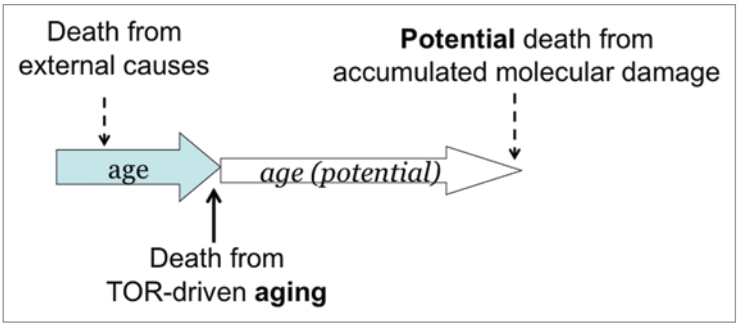

Figure 1. Actual and potential causes of death. In the wild, animals die from external causes early in life. Therefore, they do not need any brakes on TOR-driven processes. In modern humans and laboratory animals, elimination of external causes of death reveals TOR-driven aging. TOR-driven death occurs before accumulation of molecular damage becomes symptomatic. If TOR-driven aging were eliminated, then animals would undergo post-aging syndrome due to accumulation of molecular damage and unknown currently causes.

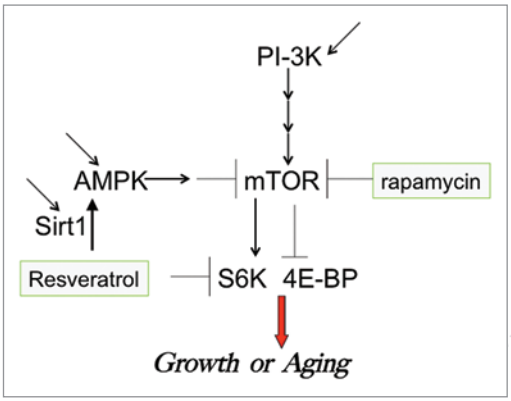

Figure 2. The TOR pathway (simplified schema). The intracellular mTOR (mammalian TOR) pathway via inputs of PI-3K, AMPK and other sensors integrates intracellular and extracellular microenvironment, nutrient availability and hormonal signals. Activation of mTOR drives mass growth and aging. Rapamacin and resveratrol inhibit the sirtuin/mTOR network.

road." (Note: just 350 years ago in London, life expectancy was less than 16 years and 75% of people born in 1662 died before they reached the age of 26 (Graunt's life table). So until recently, even humans did not preferentially die from aging. And death rate is much higher among most animals in the wild). Therefore, living beings need to grow as fast as possible to start reproduction before soma dies from external causes. The goal is to move as fast along the road as possible. Let us complete the car analogy taking into account a high death rate from external causes in the wild. Now the highway is under random artillery fire, so intense that most cars are destroyed at the beginning of the highway (childhood). The best strategy is to run at full speed, to reach a 20-mph road. And brakes are not needed. Therefore, natural selection does not favor "brakes." (Noteworthy, the natural brake is calorie restriction, which slows down both growth and aging). When external causes of death are reduced (humans, laboratory and domesticated animals), only then we notice that an organism lacks brakes (**Fig. 1**, TOR-driven aging).

TOR-Centric Model: TOR as an Engine

The TOR (Target Of Rapamycin) cellular signaling pathway senses nutrients and growth-permissive conditions.[5] The TOR pathway is universal from yeast and worms to humans and plants. In mammals, TOR (mTOR, mammalian TOR) is activated by nutrients (glucose, amino acids), insulin, cytokines, free radicals and growth factors (**Fig. 2**). In turn, TOR drives growth and aging, and aging is a continuation of growth.[2,4] Detailed discussion of the TOR pathway in aging is beyond the scope of this paper. I refer readers to the 2006 model,[2] which is not outdated at all. Since 2006, numerous predictions of the model have been fulfilled. As predicted, rapamycin and knockout of S6K1, a target of TOR, slow down aging in mice.[6,7] Rapamycin suppresses aging of human cells[8-10] and prevents aging of epidermal stem cells in mice.[11] Still awaiting its confirmation, a prediction that rapamycin could be used for prevention of all age-related diseases (from cancer to macular degeneration) by slowing down aging in humans.[2] An increasing acceptance of the role of TOR in aging has not changed so far the conventional view on aging as accumulation of random molecular damage. It is still assumed that TOR, at the end, regulates either accumulation or repair of molecular damage, thus affecting aging. Yet TOR does not regulate aging via free radicals because free radicals are simply irrelevant to aging.[12] Several recent publications further support this notion.[13-16]

Ride Slower—Get Further (Russian Proverb)

Here we compare an aging organism with a speeding car. TOR is the engine. Anything that inhibits TOR must extend life span. In fact, genetic inhibition of the TOR pathway in yeast, worms, flies and mice extends life span.[17-21] Importantly, these mutations slow aging but do not abrogate aging completely. Knockout of TOR itself is lethal early in development. In analogy, a car without the engine cannot start its journey. As already mentioned, nutrients activate TOR, thus predicting that calorie restriction (CR) would slow aging down. In fact, it is known since 1917 that CR extends life span,[22] as we now know, in almost all species from yeast to primates[23] Rapamycin (an inhibitor of TOR) is the pharmacologic brake (**Figs. 2 and 3**). Sirtuins (such as SIRT1) and their activator resveratrol, which extends life span,[24-26] antagonize the TOR/S6K pathway.[27,28] It must be noted that the "car without brakes" analogy is slightly (but

only slightly) exaggerated: genes for longevity such as SIRT1 could be considered as the brakes to certain extend. Perhaps they were not intended by nature to serve as the brakes of aging[29] and are needed to be activated pharmacologically by resveratrol for instance.[30-32]

Damage Causes Aging or Aging Causes Damage?

According to classic gerontology, aging is a decline, deterioration, loss of functions, wear-and-tear caused by all sorts of hazards such as free radicals. As often emphasized, there is no one single cause of aging but a zillion causes. Yet, loss of functions and damage are seen only at "the end of the road." This is preceded by hyper-function. In humans, aging is associated with cellular hypertension, high lipoproteins, hyperglycemia and high insulin, increased visceral fat, hyper-immunity, pro-inflammatory state, hyper-coagulation, hypertrophy and hyperplasia, enlarged prostate and growth of atherosclerotic plaques, proliferating cancer cells and an increase in aggregation-prone proteins, just to mention a few. Hyper-active and hypertrophic arterial smooth muscle cells contribute to high blood pressure, which eventually damages the organs. Hyper-active osteoclasts cause osteoporoses, eventually results in broken hip. Hyper is the key word to describe the onset of aging. Importantly, hyper-something is not necessarily higher than it was during development. But it is higher than needed. In analogy, 70 mph at the second part of the road is "hyper." Even 55 is too much. For example, in *C. elegans* protein synthesis decreases with age.[33] Yet, inhibition of protein synthesis prolongs life span.[34-36] So aging occurs not because of decreased protein synthesis but despite that. Even though protein synthesis is decreased with aging in *C. elegans*, it is not decreased enough. TOR is involved in cellular overactivation (cellular aging)[37] manifested as organismal aging and age-related diseases (hallmarks of organismal aging). Interestingly, even DNA-damage response (in the absence of DNA damage) may be a marker of cellular over-activation suppressible with rapamycin.[38]

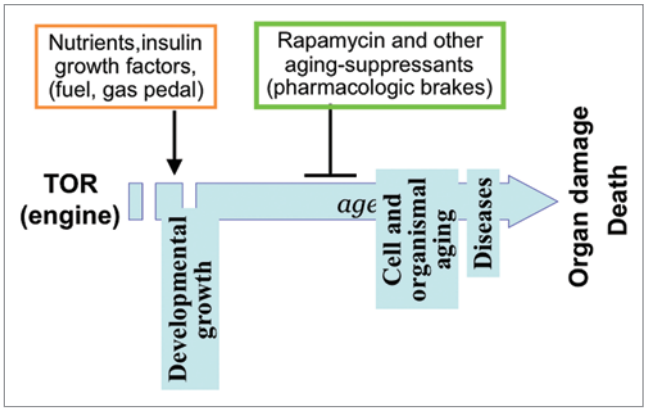

Figure 3. TOR-driven quasi-programmed aging and age-related diseases. Aging as a quasi-program (a continuation of a program for developmental growth).

Aging and Diseases

Aging is not programmed but is quasi-programmed (program-like). Quasi-program of aging is an aimless continuation of the developmental program that was not switched off. Unlike a program, a quasi-program has no biological purpose and may be harmful. In the car analogy, car may continue to move in the same direction, when a driver falls asleep. Without the brakes and with a sleeping driver, an organism is bound to be eventually destroyed. However, how this will exactly happen also depends on external events and independent genetic factors. Any particular age-related disease is caused not only by aging itself but also by external factors. Someone may die either from cancer or from myocardial infarction, for instance, depending on smoking and diet. There is a heated debate whether aging is a diseases or the norm. How would we die, if all diseases were eliminated? Do some people die from aging and others from diseases? This confusion is because it is believed that aging and diseases have different causes: aging is caused by accumulation of molecular damage, whereas each disease is caused by specific factors. But the paradox is solved, if TOR is involved in both aging and diseases of aging.[2,39,40] In fact, TOR is involved in cancer, atherosclerosis, hypertension, heart hypertrophy, osteoporosis, type II diabetes, obesity, Alzheimer's and Parkinson's diseases, age-related macular degeneration, osteoarthritis and other diseases.[2,41-43] Like crashes at the end of the road, these diseases

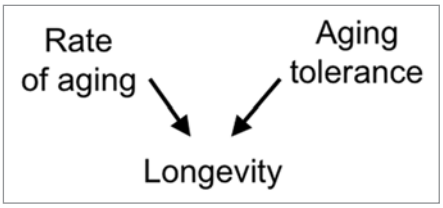

Figure 4. Increased longevity: slow aging and aging tolerance.

are late manifestations of aging. From the TOR perspective, death from aging and from diseases of aging has the same meaning, because diseases of aging are just manifestations of aging, like smoke is a manifestation of fire. In analogy, car crashes (diseases) may be consequences of over-speeding (aging). Then, does over-speeding or ostensibly the crash cause car "death?" The crash but it is caused by over-speeding. For example, myocardial infarction is a crash. Yet, the condition (atherosclerosis) that brings it about had been set in motion 40 years before the deadly event. And if an anti-aging drug were available, it would slow aging and delay atherosclerosis. Remarkably, rapamycin, a TOR inhibitor, prevents restenosis after coronary stents in humans.[44] Similarly, rapamycin prevents cancer, an age-related disease.[45-47]

What then causes death in *C. elegans* (round worm): aging or diseases of aging. Since the worm cannot attend a doctor, the answer is aging. Otherwise, age-related diseases in worm would include collapse of proteostasis, bacterial overgrowth due to autophagy insufficiency and insulin resistance.[48,49]

Extended Life Span: Slow Aging and Aging Tolerance

Life span of a speeding car can be extended not only by slowing the car down but also by designing a stronger body to tolerate damage later on the road. Similarly, life span can be extended without inhibition of the aging process. Here I introduce the term aging tolerance (or "damage-proof natural design"), which allows an organism to survive despite age-related diseases (**Fig. 4**). In the wild, organisms do not live long enough to experience aging and therefore the organism is not naturally designed to experience complications of aging too. Myocardial ischemia is the most common cause of death. In turn myocardial ischemia is caused in part by coronary atherosclerosis, which progresses with age. Life span can be extended by slowing aging, thus delaying atherosclerosis. Or it can be extended by anatomical modifications of a myocardial blood supply. (In practice, this is how bypass surgery and medical coronary stents extend lifespan without affecting aging). Occlusion of coronary artery causes life-threatening ischemia, if the ischemic zone is supplied by one artery only. A simple increase in the number of coronary arteries would prevent ischemia, when one artery is occluded. Natural selection may favor such an anatomical re-design, if it will extend reproductive life span. Humans do not reproduce often enough at the age when infarctions may occur. Otherwise natural selection would re-design coronary artery to render an organism aging tolerant. Or it would select for slower aging. Humans live longer than most mammals. Is this purely due to slow aging? For example, dogs have extensive atherosclerosis by age 8. Thus dogs age faster than humans do. Still humans may possess an increased aging tolerance (in addition to slower aging).

Medical interventions increase aging tolerance, thus extending an average life span despite chronic diseases. Yet, braking down on the aging process will prevent or delay diseases themselves. And since a continuation of TOR-driven developmental growth drives the aging process, a potential pharmacologic inhibitor is available.

Conclusion

According to classic gerontology, non-repaired molecular damage causes aging.

In contrast, we discuss here that TOR-driven process (aging) causes damage (diseases of aging). At first glance, the picture of a speeding car is frightening. Underneath, it is optimistic. From the classic perspective, nothing could be done to inhibit aging. From our perspective, the pharmacologic brake (rapamycin) will slow down human aging. While lacking internal brakes, the process could be inhibited pharmacologically, thus preventing aging and diseases of aging; and then we may very slowly age from "rusting."

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