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# Aging is not programmed

## Genetic pseudo-program is a shadow of developmental growth

Mikhail V Blagosklonny

Cell Stress Biology; Roswell Park Cancer Institute; Buffalo, NY USA

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Aging is not and cannot be programmed. Instead, aging is a continuation of developmental growth, driven by genetic pathways such as mTOR. Ironically, this is often misunderstood as a sort of programmed aging. In contrast, aging is a purposeless quasi-program or, figuratively, a shadow of actual programs.

*"The brightest flame casts the darkest shadow."*
-George Martin

### Introduction

Genes regulate lifespan, in some cases, dramatically.[1-17] Pro-aging genes encode signaling pathways such as the insulin/PI3K/TOR pathway that accelerate aging.[13-16] These signal-transduction pathways are essential for development, growth, and survival early in life.[18] Furthermore, the same signaling pathways drive cellular geroconversion: a conversion from cellular quiescence to senescence.[19-40] The same PI3K/TOR pathway is also involved in cancer and other age-related diseases.[41-44] The mTOR pathway links development and aging,[42] cellular growth and senescence,[43] robustness early in life and diseases later in life,[44,45] puberty and menopause.[46-48] Whereas development and growth are programmed, aging and diseases are not. They are aimless continuations of the program that was not switched off upon its completion. Somehow these notions are confused with programmed aging theory. As discussed,[41,49-52] it is only development that is programmed for purpose, aging is not. It is a shadow. Natural selection cannot eliminate the shadow. Nature simply selects for the brightest flame, which in turn casts the darkest shadow.

### What Are Programmed Theories of Aging

Aging and its diseases are so orderly that the explanation begs for a program. Like development, aging seems to be programmed.[53-57] Programmed theories are thought-provocative and inspiring. They brilliantly illuminate limitations of mainstream theories that aging is a stochastic, random process.[53,58] Also, while stochastic aging cannot be prevented,[59] the program can be switched off.[60-63] This makes programmed theories appealing. But why would nature program aging? It was suggested that aging is beneficial for species and groups.[53] There are conditions for group selection in humans, given that human groups had the means to exterminate each other, or using modern terms, to commit genocide. But even group selection cannot select for aging and age-related diseases. In contrast, it should select for robust soldiers, who defend the group from extermination (in human societies and social ants). It was also suggested that organisms undergo programmed death, similar to apoptosis in the multicellular organism.[64] Still, aging (at least in humans) is a decades-long process of developing age-related diseases (cancer, hypertension, diabetes, blindness) that terminate life. This is an inefficient way to commit suicide. According to programmed theories, aging prevents overpopulation, speeds up evolution, or benefits young animals, by eliminating old ("less valuable") animals. But old animals seem less "valuable" precisely because of aging. Thus, aging is programmed to eliminate less valuable animals because of aging. This is a circular reasoning. The only way out from this circle is to suggest that the aging process exists independently of a putative "suicidal program". But if so, then such a putative program is irrelevant to aging.

### Is Aging Programmed in Yeast?

Yeast death in stationary cultures, also known as chronologic senescence, may seem to be programmed.[53,65-67] Yeast secretes toxic substances (pheromones, acetic acid, etc.). If "altruistic" yeast die, then other yeast may survive. However, so-called "altruistic" yeast may be less resistant to pH and toxic substances. This simply may be a classic case of survival of the fittest (resistant) yeast. Yeast chronological aging is similar to metabolic self-destruction of human cancer cells.[68] In stationary culture, cancer cells acidify the medium with lactic acid. When most cancer cells die, a few cells may survive. Are cancer cells altruistic? In yeast and cancer cell stationary cultures, acid-resistant cells survive. The main difference is that yeast produce acetic acid, whereas cancer cells produce lactic acid.[68-72] In yeast, "oncogenic" pathways such as Ras and TOR accelerate chronological senescence.[73-75] Inhibitors of the TOR pathway, including rapamycin, decelerate chronological

Correspondence to: Mikhail V Blagosklonny; Email: Mikhail.blagosklonny@roswellpark.org, blagosklonny@oncotarget.com
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senescence in yeast.[75-77] Rapamycin decelerates "yeast-like chronological senescence" in overcrowded cancer cell culture.[68] The same signaling pathways (such as TOR) that are involved in chronological senescence in yeast are also involved in metabolic self-destruction of cancer cells.[68,73,74,78-81] The same pathways are also involved in cellular geroconversion, organismal aging, and age-related diseases (see ref. 68).

## Programmed Elements in Non-Programmed (Stochastic) Theories

Programmed theories neither specify nor predict mechanisms of death. Ironically, it was suggested that programmed aging is caused by free radicals.[53] And, vice versa, mainstream (stochastic, decay) theories accept special programs (**Table 1**). For example, it was suggested that menopause in women is purposefully programmed to stop reproduction and to raise grandchildren instead.[82] Also, it was suggested that the rate of aging is regulated by allocation of energetic resources:[83] paradoxically, the more available, the less used.[83] It is also thought that aging is programmed in Pacific salmon,[84] yet, salmon die from pathologies similar to mammalian age-related diseases. Neither aging and nor age-related diseases in Pacific salmon (or any other animals) are programmed. Aging in Pacific salmon and menopause in women are quasi-programmed.[46,85]

## Quasi-Programmed Hyperfunction (Aging)

Quasi-programmed aging is not something between "random damage" and "programmed" aging. Instead, quasi-programmed theory is absolutely different from both random damage and programmed theories (**Table 1**). According to quasi-programmed theory,[41,42,44,45,49,50,52,86-90] neither aging nor menopause is programmed, they are manifestations of the aging process, which, in turn, is a pseudo-program of developmental growth. There is a mechanistic link between mTOR-driven geroconversion, aging, and age-related pathologies, explaining how cellular hyperfunctions eventually lead to organismal death.[41]

Quasi-programmed theory predicts mechanisms of aging that are determined by mechanisms of growth, differentiation, and development. There is no need to guess what might be the mechanisms. Aging is a shadow. Its shape is determined by the developmental growth. This can be modeled in cell culture, revealing how growth can be converted to aging.

## Quasi-Program of Cellular Senescence

Nutrients, growth factors, hormones, and cytokines all activate nutrient-sensing and growth-promoting signaling pathways such as mTOR (target of rapamycin). mTOR stimulates growth and anabolic metabolism, inhibits autophagy, and increases cellular functions.[91-102] Cells grow in size, progress through the cell cycle, and then divide. In the absence of growth factors, normal cells become quiescent: they neither grow nor cycle. In When the cell is stimulated to grow, while the cell cycle is arrested, then the cell becomes senescent (geroconversion).[43] mTOR drives growth (program) and geroconversion (quasi-program) (**Fig. 1**). Also, cellular senescence can be viewed as a continuation of differentiation. The same cytokines that initially cause growth and proliferation then cause cell cycle arrest and differentiation.[103-106] During differentiation, cells acquire and amplify specific functions. One example of cellular function is secretion of cytokines, hormones, matrix, enzymes, metabolites, or lipoproteins, depending on cell type. Other examples include contraction of smooth muscle cells, adhesion, and aggregation of platelets as well as oxidative burst of neutrophils.

The same intracellular signaling pathways that initially drive proliferation, and then differentiation, also stimulate functions in differentiating cells. Cell senescence-associated hypertrophy and hyper-functions are a continuation of growth (**Fig. 1**).

**Table 1.** Comparison of 3 groups of theories of aging: programmed, stochastic, and quasi-programmed

| Theories | Defining feature | Purposeful? | Programmed? | Caused by ROS? | Kills via age-related diseases? | Causes death directly? | Menopause in women is | Link between aging and diseases | Use of energetic resources |
|---|---|---|---|---|---|---|---|---|---|
| Programmed | functional decline | yes | yes | mostly | unspecified | yes | programmed | unspecified | unspecified |
| Stochastic | functional decline | sometimes* | in some cases* | mostly | sometimes# | yes | programmed | vulnerability to diseases# | slows aging (via repair) |
| Quasi-programmed | hyperfunction | no | no | no | always | no | prototypical disease | manifested by diseases | fuels aging (via TOR) |

According to stochastic theories, aging is caused by random accumulation of damages, errors, and "garbage" due to multiple causes including but not limited to free radicals. *Stochastic theories still accept that aging can be purposefully programmed (e.g., in salmon). #According to stochastic theories, aging can kill directly (by non-specified mechanisms) and also increases the vulnerability to age-related diseases.

## From Cellular to Organismal Aging

The most relevant hallmark of cellular aging is hypertrophy/hyperfunctions and compensatory signal resistance, such as insulin resistance. Hyper-functions coupled with signal resistance cause loss of homeostasis, malfunction, organ damage, and death. The link between hyper-functions, including hypertrophy, and diseases has been discussed[41,42,50,78,107-110] and will be discussed further ("Aging: From fiction to hyperfunction", in press).

## Quasi-Program of Aging

Genetic programs determine developmental growth and the onset of reproduction. When these programs are completed, they are not switched off.

Thus, programs become quasi-programs (**Fig. 2**). Specific characteristics of quasi-programs of aging and age-related diseases were discussed in detail.[41-45,49-52,86-90] The evolutionary theory predicts quasi-programs, like it predicts genes harmful later in life, if they are useful earlier in life.[49] I emphasize that the quasi-program does not exist for its own sake: it is a shadow. Aging has no purpose (neither for individuals nor for group), no intention. Nature does not select for quasi-programs. It selects for robust developmental growth. Accelerated aging is the price for robustness.[46,50,52,88,111] Although (in some conditions) natural selection works against quasi-programs of aging, it cannot eliminate them without harming development. Genes that drive aging are needed in development. Knockout of PI3K extends the lifespan of *C. elegans* 10-fold.[12] But this comes at a price: prolonged development. Even further, disruption of the mTOR gene leads to post-implantation lethality in mice.[112-115] Whereas disruption of S6K1 extends lifespan in mice,[14] knockout of both S6K1 and S6K2 causes perinatal lethality.[116] In *Drosophila*, TOR is required for normal growth during larval development.[117]

## The Utility of the Model

Mechanisms of aging are not arbitrary but determined by mechanisms of development and growth. Since development and growth are relatively well understood, we can interpolate this knowledge to studying aging. For example, it is known that mTOR drives cellular mass growth. This predicts that p53 and hypoxia, which inhibit mTOR and cellular mass growth, will suppress geroconversion despite causing cell cycle arrest.[25,26,118-120] Thus, like other tumor suppressors,[43] p53 and hypoxia may play a dual role in aging.[121-128] The map of growth-promoting signaling network can be interpolated to aging. Gerogenes (insulin receptor, PI-3K, Akt, mTOR) and gerosuppressors (PTEN, TSC, AMPK) form a network, which (in analogy with the periodic "Mendeleev" table) predicts the effect of a particular gene on aging and diseases.[129] Basically, genes that activate the mTOR pathway are gerogenes, and those that antagonize the pathway are gerosuppressors.[43,129] As another example, developmental trends, such as an increase in blood pressure, near vision point, and FSH levels (all necessary for development and reproductive functions) cause hypertension, presbyopia, and menopause, respectively,

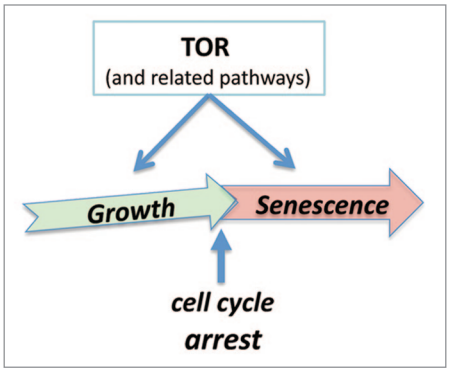


**Figure 1.** From cellular growth to hypertrophic senescence (geroconversion). Gerogenic conversion (geroconversion) from cellular growth to cellular aging, when the cell cycle is arrested. Geroconversion is a continuation of growth driven by mTOR and related pathways.

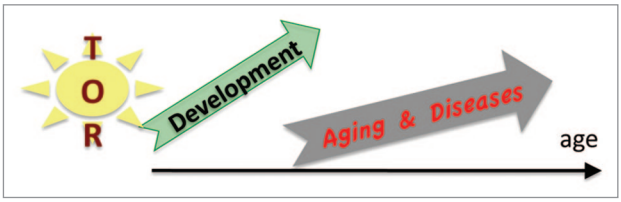


**Figure 2.** From delelopmental growth (program) to aging (shadow). Quasi-programmed aging is driven by over-activation of signal-transduction pathways such as TOR and exacerbation of normal cellular functions, which become harmful (hyper-function), leading to alterations of homeostasis, malfunctions, diseases, and organ damage.

later in life.[89] Many predictions of the quasi-programmed aging model[42] were confirmed by 2010,[87] including the prediction that rapamycin will extend lifespan in mice.[130] Numerous recent publications further illuminate the role of the mTOR pathway (and related pathways) in aging.[35,131-168]

If used properly, rapamycin improves immunity and decreases infections and their complications.[148,169,170] Under certain conditions, rapamycin can exert immunostimulatory effects, boosting T-cell responses in the face of pathogen infections and vaccines.[170,171] Rapamycin may improve response against pathogens but prevent transplant rejection.[172,173]

## Conclusion

The essence of quasi-program was discussed previously.[42,89] Here I addressed a misunderstanding that a quasi-program is a sort of a program. It is not (**Table 1**). Whereas the growth of the body is programmed, the emergence of the shadow is not. Natural selection cannot eliminate the shadow without hurting the "body". As a case in point, mTOR knockout is lethal in embryogenesis. However, pharmacologic interventions can be started in post-development, thus extending healthy lifespan. MTOR-driven quasi-program can be suppressed pharmacologically.[174] And this is what is actually important. After all, according to Oscar Wilde, *"What men call the shadow of the body is not the shadow of the body, but is the body of the soul."*

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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