Aging is programmed! (A response to Kowald-Kirkwood “Can aging be programmed? A critical literature review”)

Theodore C. Goldsmith
Azinet LLC
tgoldsmith@azinet.com
Sept 1, 2016

Abstract

Substantial and growing empirical evidence suggests that senescence in mammals is genetically programmed. However, for more than a century programmed aging was widely considered to be theoretically impossible because of the nature of the evolution process. This has resulted in multiple competing non-programmed theories that struggle to explain observations without violating Darwinian evolutionary mechanics dogma.

More recently advances in genetics have exposed major complexities in the evolution process some of which specifically enable adaptive programmed aging. Proponents now contend that programmed aging theories clearly represent the best science on mammal senescence. However, some proponents of non-programmed theories continue to argue the merits of non-programmed aging and non-programmed theories are still more popular.

This issue is important because the different theories point in very different directions regarding the fundamental nature of mammal aging and therefore research directions toward treating age-related human diseases. This article is a response to a recent article criticizing programmed aging theories and describes major deficiencies in the analysis presented in that article.

Keywords: Evolution, senescence, programmed aging, gerontology

Introduction

In their recent article (Kowald & Kirkwood, 2016) the authors (K&K) extensively criticize multiple programmed aging theories and conclude that “Non-programmed theories… are still the best explanation for the evolution of the aging process.” They do agree with programmed aging proponents that the programmed/ non-programmed issue has immense medical research importance because programmed and non-programmed theories point in very different directions regarding the nature of biological mechanisms that cause human senescence and therefore research paths toward finding ways to treat or prevent highly age-related diseases and conditions such as cancer and heart disease.

Because non-programmed theories such as the mutation accumulation theory (Medawar, 1952) or antagonistic pleiotropy theory (Williams, 1957) strongly suggest that the many very different age-related diseases and conditions are generally independent of each other, they also suggest that there is no treatable common cause of those diseases and conditions. Conversely, programmed theories suggest the existence of a common mechanism (the program) that would

contain elements susceptible to medical intervention and that therefore senescence, per se, is a treatable condition. Programmed theories therefore offer the possibility of an additional path toward treating age-related conditions that can be exploited in addition to disease-specific treatments.

We can define ***adaptive aging*** as the idea that senescence, per se, has been selected by the evolution process because internally caused deterioration and death of older members of a population produces a compensating benefit for the population. Adaptive aging theories are each based on one or more of a family of post-1962 evolutionary mechanics theories to the effect that population benefit (i.e. reduced probability of population extinction or increased probability that a species will produce descendant species) can offset some degree of individual disadvantage (i.e. reduced probability that an individual will produce adult descendants). These theories now include group selection (Wynne-Edwards, 1962), kin selection (Hamilton, 1963), gene-oriented theories (Dawkins, 1976), small-group selection (Travis, 2004), and evolvability theories (Goldsmith, 2008, Wagner, 1996). The population benefit theories were originally developed in efforts to explain *other* observations that conflicted with Darwinian mechanics such as animal altruism. In the gerontology community population benefit theories were until recently widely dismissed as theoretically "impossible" on evolutionary mechanics grounds. However, there is now a substantial theoretical basis supporting population benefit and dependent aging theories that was derived from relatively recent discoveries in genetics (e.g. Goldsmith, 2014).

We can define ***programmed aging*** as the idea that senescence is caused by an evolved logical mechanism or *program* that coordinates and stages senescence events as a function of time and other factors that logically affect the optimum lifespan for the organism. ***Regulation*** refers to the ability of a biological program to alter genetically specified parameters within some range in response to changes in internal or external conditions that affect the optimum operation of the program. Regulation necessarily entails the ability of the organism to *detect* or *sense* the relevant conditions.

Regulated programmed mechanisms are ubiquitous in biology. Aging could therefore be controlled by a regulated programmed mechanism similar to the one that controls reproductive parameters such as age at reproductive maturity, mating season timing and duration, litter size, and gestation time. For comparison purposes we can examine a proposed regulated programmed aging concept (Fig 1) in which a single logical control mechanism capable of detecting internal and external conditions that affect the optimum lifespan for a species would then control the expression of senescence in various tissues by means of signaling. In this particular concept (Goldsmith, 2013) the system causes senescence by down-regulating maintenance and repair mechanisms that act to prevent the corresponding age-related diseases (more below). Because it is clear that reproductive parameters affect the lifespan needed by an organism and that reproductive parameters are themselves affected by external conditions and determined by a regulated program, we would expect coordination between reproductive parameters and senescence. Many temporary or local conditions (e.g. predation, famine), affect optimum lifespan (Goldsmith, 2014), contributing to the benefit of regulation.

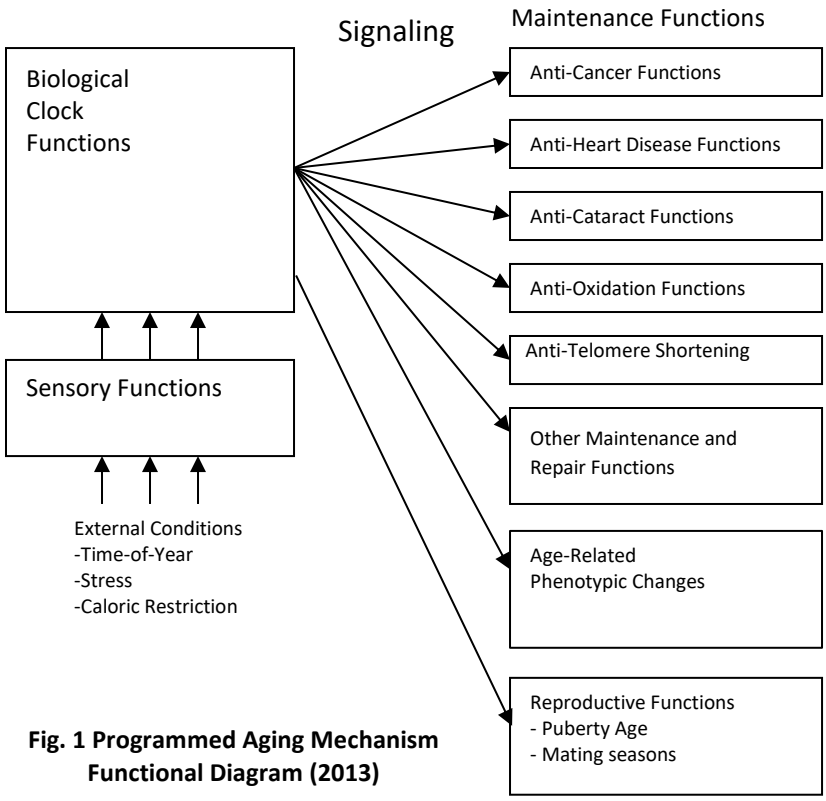

Fig. 1 Programmed Aging Mechanism Functional Diagram (2013)

Many biological clocks are themselves obviously implemented by regulated mechanisms that detect external cues (e.g. circadian rhythm, mating seasons).

This model suggests that there are three general paths toward treating an age-related disease: We can repair or prevent damage; we can enhance the corresponding anti-disease mechanism (e.g. by enhancing immunity in cancer therapy); or we can interfere with the common control mechanism (e.g. by interfering with signaling, clock, detection schemes, or other elements).

Adaptive theories logically lead to the existence of an aging program because they assume an evolutionary need to both attain but not exceed some particular species-specific *optimum* lifespan. However, programmed aging is not necessarily adaptive in the sense that senescence, per se, is the selected parameter as described further below.

The evolutionary nature of senescence emerged as a problem shortly after publication of *Origin* (Darwin, 1859) and there is still no agreement on a solution. In 1952 Medawar proposed a modification to Darwin's evolutionary mechanics to the effect that the force of evolution declines with age because of attrition due to external causes and that consequently senescence has only a small effect on a wild population (Medawar, 1952). This concept is important to modern programmed and non-programmed theories.

Major Issues with K&K analysis

Modern adaptive programmed aging theories date from 1988 (Libertini, 1988). Modern evolvability theories are even more recent (Wagner, 1996). However, K&K place much importance on earlier analysis purporting to prove the fallacy of group selection e.g. (Maynard Smith, 1976). They also give major credence to popularity as opposed to current science e.g. "The idea that aging is a programmed trait was first articulated by Weismann (1891) but is now generally accepted to be wrong..." and similar statements (Kowald & Kirkwood, 2016). Inevitably older concepts will be more popular, especially if people are still taught to believe them.

The K&K conclusion is heavily based on "math model" and simulation analysis in which all of the assumptions are not stated and some are incorrect (see below). Such analysis of this subject is very difficult. Darwin suggested that the evolution process is very incremental and occurs in "tiny steps" (Darwin, 1859). This in turn implies that the evolution process is capable of selecting between "tiny" differences in fitness. This leads to a situation in which theorists are "comparing different values of zero." Example: does the (possibly tiny) evolvability or group advantage of senescence offset its (possibly tiny) individual disadvantage? Some discussions on the evolutionary nature of aging resemble arguments as to how many angels can fit on the head of a pin!

The K&K analysis extensively reports on purported flaws in various programmed aging theories. However, it makes no attempt to respond to major criticisms of *non-programmed theories* (Goldsmith, 2013, Libertini 2015, Skulachev, 2011). Many such criticisms suggest existence of implausible assumptions concerning the nature of non-programmed aging *mechanisms* and implausible explanations for non-mammal observations such as non-senescent species (Goldsmith, 2013). Obviously, a credible comparison would need to assess these published issues. Note that there is still no agreement among the non-programmed faction as to which *non-programmed* theory is correct and the theories attack each other (e.g. Kirkwood, 2011).

K&K make the common mistake that evolvability is merely a form of group selection and can therefore be dismissed based on 40-year-old analyses such as (Maynard Smith, 1976). Worse, since evolvability can be seen as benefitting a species, evolvability could be equated to "species-level group selection" widely seen as the most implausible of the "group" concepts. As also described by K&K, an issue with the group concepts is the idea that a future (group) benefit such as non-extinction of the group must be discounted relative to a present (individual) cost. This problem is progressively worse as the size of the group and consequently the time difference between cost and benefit increases. This leads to theorists who believe in "kin" selection or "small isolated group" selection but not "species-level group" selection. As described extensively elsewhere (Goldsmith, 2014), the logic behind evolvability is substantively different. Evolvability benefits the evolution process, applies to any size group, and does not suffer from the present/future problem.

Criticisms (and analysis) of the various "levels" of group selection are based on the future vs present issue mentioned above. However, Williams suggested that the nature of a particular genomic design could result in permanently *genetically linking* an individually adverse trait (like

senescence) to some individually beneficial trait(s) in such a way as to make it impossible for the evolution process to eliminate aging without also removing a trait that provided benefit in earlier life (Williams, 1957). If the net benefit of the linked traits was positive, both would be retained. This is the non-programmed *antagonistic pleiotropy* (AP) theory. The permanent linkage would protect senescence from being removed even though it continuously represented an individual disadvantage at least since the emergence of animals. Since then many other types of genetic linkage have been identified (Goldsmith, 2014) that can be expected to have different durations (or "robustness", or "rigidity" i.e. require different amounts of time for the evolution process to separate the traits and produce the benefit without the disadvantage). Such linkages could protect an individually adverse trait for long enough to allow the group benefit to be obtained. Note that this concept is more plausible than the AP theory because it does not require the linkage to be permanent. In other words antagonistic pleiotropy works better for adaptive aging (senescence has a population benefit) than it does for non-adaptive aging (senescence has only cost). Any credible analysis or model would need to incorporate these concepts or show why they are invalid.

Programmed disposable soma theory: It is widely agreed that organisms possess many different "maintenance and repair" (M&R) mechanisms that act to offset corresponding damage mechanisms. Wounds heal, infectious diseases are combatted, and dead cells are replaced, requiring very different evolved mechanisms to accomplish these different functions. There would correspondingly exist an anti-cancer mechanism that acted to prevent cancer and different M&R mechanisms corresponding to other age-related diseases and deteriorative conditions.

There is little disagreement that M&R activities require energy and material resources. Indeed, it has been suggested that because of the declining value of survival (Medawar, 1952) an organism would logically want to reduce maintenance and repair activities as a species-specific function of age and use the released resources to enhance reproductive fitness i.e. the disposable soma theory (Kirkwood, 1977). Conversely it has been suggested that an adaptive aging program could operate by down-regulating maintenance and repair functions (Goldsmith, 2013) Fig 1.

Unsurprisingly, K&K have not argued against the disposable soma theory. Nor have they argued against the idea that a *regulated programmed aging mechanism* such as Fig. 1 would provide the best implementation of the disposable soma concept (Goldsmith, 2015). Indeed K&K allude to the idea that adjustment of lifespan in response to local conditions "could be adaptive." Perhaps this is mainly a semantic issue and programmed aging by any other name is still programmed aging!

Conclusion

Funding for any medical research project is essentially an informed wager. People making such wagers, having reviewed the *current* literature or even just the K&K article, would find that there is substantial scientific disagreement on the fundamental programmed/ non-programmed nature of aging, that the disagreements are based on arcane and difficult theoretical issues, and that there is wide agreement that the theories point in different medical research directions. Many non-science factors act to prevent consensus on the nature of aging (Goldsmith, 2014). The ~150 year history of these issues also suggests that waiting for a strong academic consensus is not an

option. Therefore a rational research manager would tend to pursue both concepts. Such diversification has already begun (Goldsmith, 2014).

References

Darwin C (1859) On the Origin of Species by Means of Natural Selection. London John Murray

Dawkins R (1976) The Selfish Gene. Oxford University Press.

Goldsmith T (2008) Aging, evolvability, and the individual benefit requirement; medical implications of aging theory controversies. J. Theor. Biol. **252**. 764-768.

Goldsmith T (2013) Arguments against non-programmed aging theories. Biochemistry (Mosc) 78, 971-978.

Goldsmith T (2014) The Evolution of Aging 3rd ed. Annapolis Azinet Press

Hamilton W (1963) The Evolution of Altruistic Behavior, American Naturalist 97:354-356.

Kowald A, Kirkwood T (2016) Can aging be programmed? A critical literature review. Aging Cell doi: 10.1111/acel.12510

Libertini G (1988) An adaptive theory of increasing mortality with increasing chronological age in populations in the wild. J. Theor. Biol. **132**. 145-162.

Libertini G (2015). Non-programmed versus programmed aging paradigm. Curr. Aging Science 8(1):56-68

Maynard Smith J (1976) Group selection. Quart. Rev. Biol. **51**, 277-283.

Medawar P (1952) An Unsolved Problem of Biology. London: H.K. Lewis.

Skulachev V. (2011) Aging as a particular case of phenoptosis, the programmed death of an organism. (A response to Kirkwood-Melov "On the programmed/ non-programmed nature of aging within the life history"). Aging (Albany NY) 2011

Travis J (2004) The Evolution of Programmed Death in a Spatially Structured Population. Journal of Gerontology 2004 59A 4 301-305.

Wagner G, Altenberg L (1996) Perspective: Complex adaptations and the evolution of evolvability. Evolution 50:3

Weismann A (1891) Essays upon heredity and kindred biological problems 2nd ed. Oxford Clarendon.

Wynne-Edwards V (1962) Animal Dispersion in Relation to Social Behaviour, Edinburgh: Oliver & Boyd, 1962

Wynne-Edwards, V (1986) Evolution Through Group Selection, Blackwell. ISBN: 0-632-01541-1

Williams G (1957) Pleiotropy, natural selection and the evolution of senescence. Evolution **11**, 398-411