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Emerging programmed aging mechanisms and their medical implications

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ABSTRACT

For many generations programmed aging in humans was considered theoretically impossible and medical attempts to treat or delay age-related diseases were based on non-programmed aging theories. However, there is now an extensive theoretical basis for programmed mammal aging and substantially funded medical research efforts based on programmed aging theories are underway. This article describes the very different disease mechanism concepts that logically result from the theories and the impacts emerging programmed aging mechanisms will have on funding and performing medical research on age-related conditions.

Introduction

There are two modern evolutionary theories of aging: modern *non-programmed aging theories* (e.g. [1–3]) are based on the idea that each species has an evolutionary need to survive and reproduce for a particular species-specific period and that beyond that period there is no net evolutionary advantage from being capable of further survival and reproduction. The force of evolution is toward developing a particular *minimum* internally-determined lifespan for each species and there is no net advantage or disadvantage from living longer.

Modern *programmed aging theories* agree that there is a species-specific age at which the evolutionary need to survive and reproduce declines to zero but contend that beyond that age there is a net evolutionary *disadvantage* from further survival and reproduction. The force of evolution is toward developing a particular *optimum* lifespan because a lifespan that is either too short *or too long* creates an evolutionary cost. An *aging program* is understood to mean an evolved biological mechanism (adaptation) that purposely limits individual lifespan.

Both theories depend on a modification to Darwin's survival-of-the-fittest idea introduced by Medawar in 1952 [1] to the effect that the force of evolution declines beyond the age at which an organism is able to complete an initial reproduction and that therefore the evolutionary need for further survival and reproduction also declines following that age. Medawar supposed that under wild conditions mortality due to *external* causes would progressively reduce the size of an age-cohort and therefore reduce the evolutionary benefit of having the *internal capability* for living longer. For example, there would be no evolutionary benefit from having the internal capability for living longer than age *X* if essentially no individuals survived beyond age *X* because of external causes.

Many species-dependent factors determine the internally determined lifespan needed by a species including internal programmed reproductive parameters such as age at puberty, timing and duration of mating seasons, duration of gestation, and degree of parental nurturing. External factors that can be temporary or local also alter lifespan requirements such as degree of predation, harsh environment, overcrowding, and famine.

In mammals, programmed theories generally (see exception below) depend on an additional modification to Darwin's idea in the form of one of the *population benefit theories* introduced beginning in 1962 and including group selection [4], kin selection [5], gene-oriented theories [6], and evolvability theories [7,8]). These theories suggested that long-term *population benefits* (e.g. reduced probability that a population would become extinct or increased probability that a species would produce descendant species) could offset *individual disadvantage* (i.e. reduced probability that an individual organism possessing a particular phenotypic design would produce adult descendants) and allow the evolution and retention of an individually-adverse trait. These theories were engendered by observations *other than aging* (such as *animal altruism*) that appeared to conflict with Darwin's natural selection theory.

Starting in the 1980s theorists then proposed [9–12] at least a dozen population benefits that would result from a purposely limited lifespan. Historical objections to these proposals were mainly based on the idea that evolutionary processes such as those

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Table 1
Summary comparison of modern non-programmed and programmed aging theories.

	Non-programmed	Programmed
Evolutionary basis	Darwin + Medawar	Darwin + Medawar + population benefit theory
Aging theory history	1952+	1988+
Anti-aging medicine	Infeasible	Feasible
Accommodates local and temporary conditions	No	Yes
Matches empirical evidence	Some match	Best match

involved in propagation of mutations would not support evolution and retention of an even slightly individually-adverse trait regardless of any population benefit, i.e. *all* of the population benefit theories were *totally* invalid. However there are now multiple proposed solutions to the evolutionary mechanics issues [8] and such objections have waned.

Programmed and non-programmed ideas, when combined with observations, logically lead to very different concepts regarding the biological mechanisms responsible for aging in mammals including humans.

Because of its long-term, diffuse, and multi-system nature, aging is a very difficult subject for medical research [13] and therefore aging theories and their predicted aging mechanisms are very important in suggesting research directions (see Table 1).

This article presents functional models for the different aging mechanisms that logically follow from the two theories and discusses their implications for medical research and public health.

Non-programmed aging mechanisms

A functional model for non-programmed aging mechanisms is shown in Fig. 1. It is widely agreed that mammal aging has many different manifestations including cancer, heart disease, stroke, arthritis, cataracts and other sensory deficits, muscle weakness, and decreased immune response, all of which can be considered deteriorative in that they reduce an individual organism's ability to survive and reproduce. It is clear that the proximal cause of each manifestation is different deteriorative processes and that these processes can differ even between different types or sub-types of cancer or other manifestation of aging. These processes can also involve oxidation, free radicals, radiation damage, pathogens, and mechanical wear and tear.

It is also apparent that living organisms possess many anti-deterioration mechanisms that act to offset the deteriorative processes. Wounds heal, dead or damaged cells are replaced, and infections are resisted. Because the deteriorative processes vary greatly between manifestations, the corresponding anti-deterioration mechanisms must also vary greatly. According to non-programmed theory, for each deteriorative process, there would only exist an evolutionary motivation to evolve and retain a corresponding anti-deterioration mechanism that was capable of delivering the needed species-specific minimum lifespan.

This model provides a good match to two major observations about aging: First it explains why different mammal species have such large differences in internally determined lifespans despite being biochemically very similar and therefore being similarly susceptible to the deteriorative processes. Mammal lifespans vary over a range of more than 200 to 1 from less than one year (Argentine desert mouse) to more than 200 years (Bowhead whale) [14]. Second: it explains why *manifestations* of aging are very similar between different mammal species. For example, canines and humans share very similar manifestations of aging but at very different ages leading to very different lifespans. The deteriorative processes are similar but the corresponding anti-deterioration mechanisms are each less effective in shorter-lived species.

Efforts toward medical intervention in a particular age-related disease based on this model involve attempts to prevent or repair damage from its deteriorative processes or attempts to enhance the anti-deterioration processes associated with that disease.

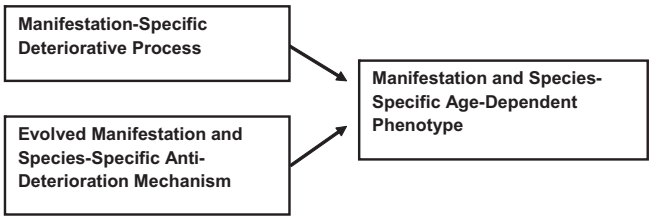

Fig. 1. Non-programmed concept for the biological mechanism responsible for each of many different manifestations of aging. The combined effect of a manifestation-specific deteriorative process and an evolved manifestation and species-specific anti-deterioration mechanism produces the species and age-dependent phenotype associated with that disease or condition.

Programmed aging mechanisms

Programmed aging theories suggest that aging is a biological function that serves an evolutionary purpose by limiting organism lifespans in order to obtain a species-unique *optimum* lifespan. Fig. 2 shows an evolved biological senescence control mechanism that logically follows from the evolutionary need to produce an optimum lifespan that can be adjusted to accommodate temporary or local conditions that affect optimum lifespan.

A *clock function* determines the nominal genetically determined age at which senescence should occur for a particular species.

Sensing of internal or external conditions that affect optimum lifespan allows for adjustment of individual lifespans to accommodate local or temporary conditions.

A *logical process* determines how to respond to the local or temporary conditions and the rate at which senescence should occur for a particular species.

Signaling allows coordination of activities between various tissues in order to execute the senescence function. Signaling can be accomplished by the nervous system in addition to chemical signals (hormones and even pheromones). The octopus suicide mechanism involves the nervous system [15] and hormone-directed lifespan control mechanisms have been discovered in *C*aenorhabditis *elegans* (J. Apfield, C. Kenyon, C. Wolkow [16–18]). In this senescence mechanism model, which represents an extension of the non-programmed mechanism, signals down-

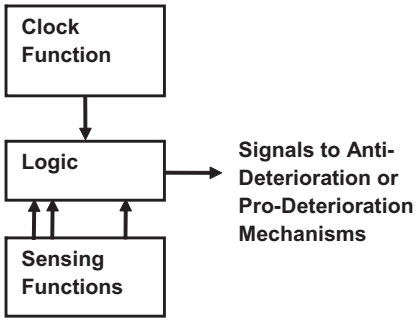

Fig. 2. Programmed senescence control mechanism – an aging program coordinates senescence activities in various tissues by means of signals that regulate anti-deterioration mechanisms and can vary expressed senescence depending on local or temporary conditions.