Senescence as a defense strategy against parasites

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The teleology of aging has been one of the more vexing and controversial question in biology. While the prevailing view of aging as a non-programmed, degenerative process has been challenged by recent discovery of genes that appear to influence the rate of aging and of interventions such as parabiosis and microbiome transfers that appear to reverse some features of aging, a convincing explanation for why programmed senescence might be evolutionarily favored has been lacking.[1,2,3, 4,5] Here we describe stochastic simulations of host and parasite populations with senescence as an independent variable. The results show that populations with more rapid senescence bear lower parasite loads and oscillate more quickly through alternate phenotypes with differential resistance against parasites. We conclude that programmed aging and death may promote host evasion of parasites in a co-evolutionary competition against parasites.

If aging is a programmed process rather than a non-programmed degenerative process., then there are significant implications for the direction of anti-aging research and aging may be a more tractable disease than previously believed.

According to the Red Queen hypothesis, sex evolved as a mechanism for periodically changing the host defense mechanisms against parasites, in face of parasites' adaptability to those defense mechanisms.[6] There is supportive evidence that strains of parasites and host susceptibility to the strains may cycle in a periodic fashion.[7,8] If oscillatory evolution is a key constituent of successful arms race against parasites, the oscillatory period may be important variable in the strategy. The faster the host can cycle through the repertoire of defensive genetic combinations, more easily it may be to evade the parasite. It stands to reason that rapid senescence post reproduction may accelerate the cycling of the host parasite resistance phenotypes. In fact, in both semelparious and iteroparious organisms, senescence may be triggered by reproduction.[9,10,11,12,13,14] Furthermore, given that aging is generally, although not exclusively, limited to multicellular sexually reproducing organisms, it is reasonable to hypothesize that the evolutionary pressures that led to sex also may be involved in aging.

We therefore postulated that parasite defense may be a reasonable teleological explanation of programmed aging. Programmed senescence may be an important variable in the effectiveness of the sex-based parasite defense system, because the periodicity of the defense cycles and the effectiveness of the cycling in reducing parasite burden may be influenced by lifespan of the hosts.

The model assumes a fixed population, with three phenotypes of hosts and three phenotypes of parasites. Each host phenotype is completely resistant to infection against one parasite phenotype, partially resistant to a second parasite phenotype, and not resistant to one phenotype in a cyclic fashion, such that host phenotype A is completely resistant to parasite phenotype A and partially resistant to parasite phenotype C; host phenotype B is completely resistant to parasite phenotype B and partially resistant to parasite phenotype A; and so on. This assumption is consistent with previously described cyclic resistance pattern.[7]

Each host is assumed to be at risk for dying each year, based on a base rate of non-senescence mortality and after reaching a predefined age of senescence, a rate of senescence rate of death based on an inverse of age of senescence. Each host that dies is replace by a new host,

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whose phenotype is based on the population distribution of the phenotypes in the population the prior year, modified by reproductive penalty for hosts that are infected, and also modified by a fixed regeneration factor that simulates recombination due to sexual reproduction. The regeneration factor allows for regeneration of phenotypes even when they have disappeared from the population, consistent with the theory proposed by Hamilton that alleles with transient low fitness is stored and not eliminated, to be re-expressed at a subsequent date.[6] Each uninfected host can be infected by a parasite, determined by a transmission rate. The phenotype of the parasite for the infection is determined by the distribution of parasite phenotypes in the prior year, modified by a fixed regeneration factor that simulates recombination due to sexual reproduction. If the host was resistant to the parasite phenotype, then the likelihood of infection was modified by the resistance factor. Each host was permitted to be infected by one parasite strain at a time.

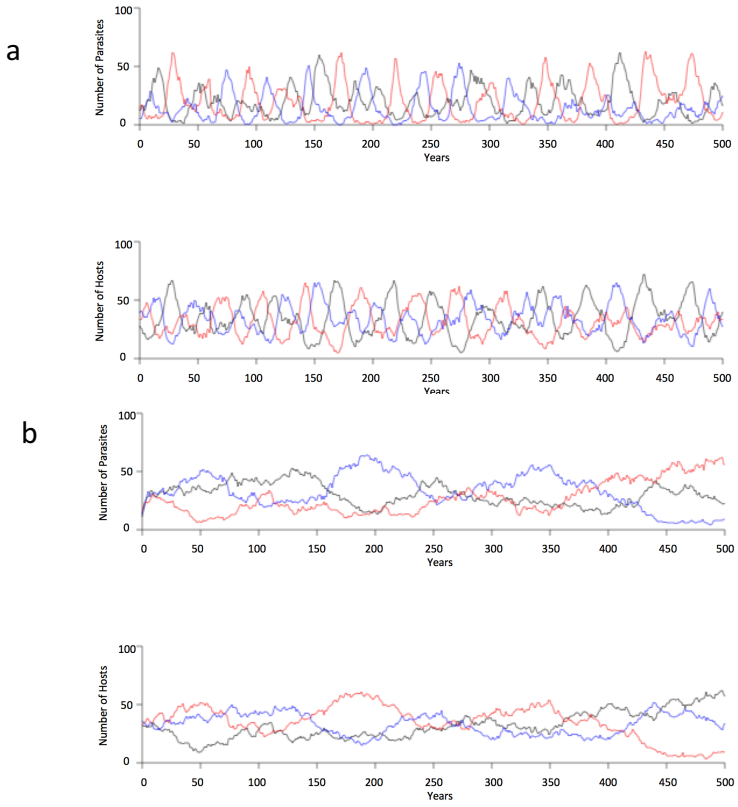

Figure 1 | Stochastic simulations of host and parasite populations. a. Simulation with 2-year onset of senescence. The top graph is the parasite population, and the bottom graph is the host population. Vertical axis is the number of organisms, and the horizontal axis is the years. Each color represents one of three phenotypes. The corresponding color on the graphs represents one parasite phenotype and the host phenotype that is resistant to the parasite phenotype. **b.** Simulation with 20-year onset of senescence.

Figure 1a and 1b illustrates how the simulation based on 2-year senescence onset compares to a simulation based on 20-year senescence onset. While both populations cycle through the host

and parasite phenotypes, the periodicity of the oscillations in the 2-year senescence simulation is consistently shorter.

	2-Year	5-Year	10-Year	20-Year
Average Parasite Load	59.20%	80.93%	87.62%	90.39%

Table 1 | Average Parasite Load. The mean parasite load, as measured by percentage of hosts that are infected in each year for each of the simulations, after 1,000 iterations of 500-year simulations.

Table 1 illustrates the average parasite load after 1,000 iterations of the simulation for the 2-year senescence onset population and the 20-year senescence onset population. As hypothesized, the population with shorter lifespan yielded substantially lower overall parasite burden.

Our model suggests that under a certain set of assumptions, decreased lifespan can result in lower parasite load, along with more rapid oscillation of parasite resistance phenotypes. The decrease in oscillation period and decrease in parasite load may have a causal relationship, and support the hypothesis that if senescence is an adaptive, programmed trait, then evolutionary pressure from parasites may be a factor driving its pervasiveness, much as it may have been the factor driving the evolution of sexual reproduction.

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