MINI-REVIEW

When and How Can Death Be an Adaptation?

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Abstract—The concept of phenoptosis (or programmed organismal death) is problematic with respect to most species (including humans) since it implies that dying of old age is an adaptation, which contradicts the established evolutionary theory. But can dying ever be a strategy to promote fitness? Given recent developments in our understanding of the evolution of altruism, particularly kin and multilevel selection theories, it is timely to revisit the possible existence of adaptive death. Here, we discuss how programmed death could be an adaptive trait under certain conditions found in organisms capable of clonal colonial existence, such as the budding yeast *Saccharomyces cerevisiae* and, perhaps, the nematode *Caenorhabditis elegans*. The concept of phenoptosis is only tenable if consistent with the evolutionary theory; this accepted, phenoptosis may only occur under special conditions that do not apply to most animal groups (including mammals).

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PROGRAMMED AGING AND PHENOPTOSIS

Is aging programmed? Asking this question risks falling afoul of the old warning: ask a stupid question and you'll get a stupid answer [1, 2]. This is because the term *programmed aging* has multiple meanings, which can lead the questioner into logical confusion [3]. But it is possible to disambiguate this term and to avoid conceptual pratfalls, as follows. In *programmed aging*, the word *aging* can refer to all age changes (including benign, maturational changes) or specifically to age-related deterioration (or *senescence*, not to be confused with *cellular senescence*, *sensu* Hayflick). It is safe to say that the intended meaning of *programmed aging* is *programmed senescence*, at least usually.

The word *programmed* is trickier. In biology, *programmed* can mean involving concerted, gene-regulatory or developmental changes, controlled by genes, gene-regulatory networks and signaling pathways. Also implied here is that a program is *for* something, serving a purpose in terms of increased fitness in the evolutionary sense. For convenience, we will refer to these two meanings as programmed in the *mechanistic* sense and *adaptive* sense, respectively.

In the context of senescence, it is notable that biological processes are

sometimes programmed in the mechanistic sense but not in the adaptive sense, and that this can promote pathology. For example, a mechanistic program for the cell cycle executed within metastatic melanoma cells impairs rather than promotes organismal fitness. To improve the clarity of meaning, M. V. Blagosklonny introduced the term *quasi-program* to denote situations where a program is executed in a fashion that does not promote fitness, e.g., due to accidental initiation, or futile continuation after its purpose has been fulfilled [4]. Accordingly, we will refer to adaptive and non-adaptive programmed aging as programmed and quasi-programmed aging, respectively.

Phenoptosis is another relatively new term to describe programmed organismal death resulting from programmed aging, in both mechanistic and adaptive senses [5]. However, the claim that senescence and consequent death promote fitness is not consistent with the mainstream evolutionary theory, at least not as applicable to most organisms [3]. As described below, the theory predicts that selfish, non-dying variants would outcompete their altruistic aging counterparts. This standard view of living organisms as bourgeois means that the concept of phenoptosis carries a heavy burden of proof, both empirical and theoretical. But could proof be found?

The relative lack of empirical evidence may reflect the technical difficulties involved, at least in part. Measuring individual fitness is relatively straightforward; for example, one can readily measure how the presence or absence of programmed cell death (apoptosis) affects fitness markers such as organismal growth and reproduction. By contrast, it is difficult to measure benefits at the level of group selection and inclusive fitness, and to distinguish them with certainty from individual fitness benefits. Regarding theory, it is possible that adaptive death (phenoptosis) can evolve under certain permissive conditions, particularly where organisms exist as clonal, viscous (i.e., high density) populations, where the distinction between individuals and the colony is blurred, as discussed next.

WHERE EVOLUTIONARY THEORY PREDICTS ADAPTIVE DEATH

Central to the evolutionary theory of aging is the understanding that the effects of natural selection decline with increasing age, and that this leads to the accumulation in the inherited genome of gene variants with deleterious effects in later life [6-8]. Here, the original concept was that such variants are simply deleterious, late-acting mutations [9]. A later and better-supported view is that such variants act throughout the life history, enhancing fitness in earlier life and promoting pathology in later life (exhibiting so-called antagonistic pleiotropy) [10]. A major prediction of this theory is that senescence *per se* is not an adaptation, but rather an accidental side effect of various traits and processes that promote fitness earlier in life, which is inconsistent with the concept of phenoptosis.

However, despite the cogency and explanatory power of the evolutionary theory of aging, some phenomena sit uncomfortably with it. One example is the existence of single gene mutations that cause large increases in lifespan in the nematode *Caenorhabditis elegans* [11]. In some minds, this has raised the question: could natural selection favor wild-type alleles *because* they cause earlier death? This in turn leads us to wonder: could *C. elegans* experience unusual evolutionary conditions that somehow enable death to promote inclusive fitness [3]?

It was originally suggested in the 19th century that aging is favored by

natural selection because by causing death it eliminates old and unfit individuals, thereby increasing the availability of resources for younger generations [12]. However, this hypothesis relies on group level selection and is therefore not predicted to be an evolutionary stable strategy. The issue here is that the individual selective advantage for non-aging cheaters is predicted to far exceed the inclusive fitness benefits of self-sacrifice [1, 10].

One counter-argument in support of phenoptosis reasoned that because there are genes (e.g., p53) that promote aging or, if mutated, cause disease (here cancer), this implies that mutations cannot lead to the accumulation of non-aging cheaters [13, 14]. However, more plausibly, this is an example of antagonistic pleiotropy, since p53 reduces accumulation of mutated, potentially cancerous cells in young animals, but can accelerate aging in later life, e.g., by increasing accumulation of senescent cells. Phenoptosis was also proposed to promote fitness due to the benefits arising from accelerated evolution under unfavorable environmental conditions that increase mutation rate (the evolvability hypothesis) [5]. It has been argued, though, that the evolvability hypothesis is problematic insofar as it requires unrealistic conditions (either too high a rate of appearance of beneficial mutations or too rapid changes in the environment [15, 16]) for it to be widely applicable.

However, it remains possible that phenoptosis could evolve under certain circumstances. The studies of the last decade suggest that the impact of group and multilevel selection has previously been underestimated [17, 18], including in the context of aging [19-25]. Drawing on the classic evolutionary theory, we have previously discussed how senescent death could evolve as an adaptive group trait in species that exist in populations with a high coefficient of relatedness (particularly, clonal populations) and low dispersal level [3]. These two critical conditions generate a selective environment with relatively high inclusive fitness benefits to family members, consistent with Hamilton's rule $rB > C$, where r is the coefficient of relatedness, B is the benefit to the recipient, and C is the cost to the donor [26]. One organism that potentially fulfils these conditions is the nematode *C. elegans*, suggesting that adaptive death could occur in this species [3]. This raises the possibility that, to some degree, long-lived *C. elegans* mutants are akin to apoptosis-defective cells (loss of programmed death).

Important to the definition of adaptive death is that death itself must promote fitness rather than merely being a cost coupled in a trade-off with the fitness component. Indeed, there are multiple cases where death occurs immediately as a consequence of fitness-promoting behavior, but the death event itself confers no advantage. For example, when a honeybee stings a human, her brave defense of the hive may increase her inclusive fitness, but her consequent death does not. Here, the death is not adaptive but an immediate cost and a side effect; by the same token, aging is a side effect of selection on earlier age classes according to the evolutionary theory of aging. One argument commonly used in favor of phenoptosis is the existence of species in which death occurs rapidly after reproduction, e.g., *Octopus hummelincki* or males of Macleay's marsupial mouse *Antechinus stuartii* [27]. However, a more plausible explanation for such semelparous reproductive death is that it is a cost coupled to intense reproductive effort.

We have distinguished several forms of adaptive death based on the means by which they promote inclusive fitness (figure, panels (b)-(d)) [3]. First, *consumer sacrifice*, where death promotes fitness by reducing competition for food and other resources. Second, *biomass sacrifice*, where death facilitates post-mortem transfer of resources from a parent to kin,

particularly progeny. Third, *defensive sacrifice*, where death protects kin from an attacker, for example by preventing the transmission of a pathogen to kin.

{Figure} Adaptive death and forms it can take. a) When organisms that can exist as independent individuals associate into social entities with super-organism-like features, programmed death can increase inclusive fitness. For death to be adaptive, it must provide a benefit to kin or the (super)-organism, rather than merely be a cost resulting from a beneficial trait. b) In consumer sacrifice, death of older individuals results in fewer mouths to feed, increasing resources for kin. This could, in theory, increase inclusive (or colony-level) fitness in *Caenorhabditis elegans*, which has a boom-and-bust lifestyle and a very short reproductive period [3]. c) Biomass sacrifice occurs when parents (individuals or cells) die to facilitate transfer of nutrients from their own biomass to kin. In *Saccharomyces cerevisiae*, programmed cell death is believed to promote growth elsewhere in the yeast colony through the release of nutrients [35]. d) In defensive sacrifice, death increases the chance of kin survival in case of enemy attack. A possible example is the protozoan parasite *Leishmania* spp., where programmed cell death has been suggested to reduce the host immune response against kin [36]

ADAPTIVE DEATH IN UNICELLULAR ORGANISMS: APOPTOSIS AS PHENOPTOSIS

Probably the best evidence for adaptive death comes from the occurrence of programmed cell death in organisms that may be considered as unicellular. Programmed cell death in unicells involves a conserved genetic pathway that suggests that it evolved before the appearance of multicellularity [28-30]. On the face of it, this is paradoxical in terms of the classic evolutionary theory, since programmed cell death in unicellular organisms is also programmed organismal death. This phenomenon has been well studied in the budding yeast *Saccharomyces cerevisiae*, where the pathways involved have been described [31-33] and the evolutionary significance explored [5, 22, 34].

This paradox may be resolved by considering that *S. cerevisiae* in the wild often grow as viscous, clonal colonies, where older cells die apparently to provide resources for their younger and more actively dividing sibling cells [35] – an example of biomass sacrifice adaptive death (figure, panel c). Here, programmed cell death can be seen as a mechanism to increase the fitness of the yeast colony as a whole, much as apoptosis in metazoans benefits organismal fitness. If correct, this would imply that programmed cell death in yeast has not evolved as programmed organismal death (i.e., not as phenoptosis) [16], at least insofar as its function is to promote colony level fitness.

In summary, we have described how the classic evolutionary theory can, under rare circumstances, allow for the occurrence of genuine adaptive death, equivalent to phenoptosis. The concept of phenoptosis is derived from that of apoptosis, which is able to promote fitness because of the social interaction of clonal cell populations in multicellular organisms and action of natural selection at the level of multicellular individuals. Likewise, the conditions necessary for phenoptosis to occur (viscous clonal populations) are those where groups of individuals possess features of higher order individuals,

or super-organisms (figure, panel a). In such contexts, it is arguable whether programmed death is that of an individual or of a component of a higher-order individual, such as a bacterial or yeast colony.

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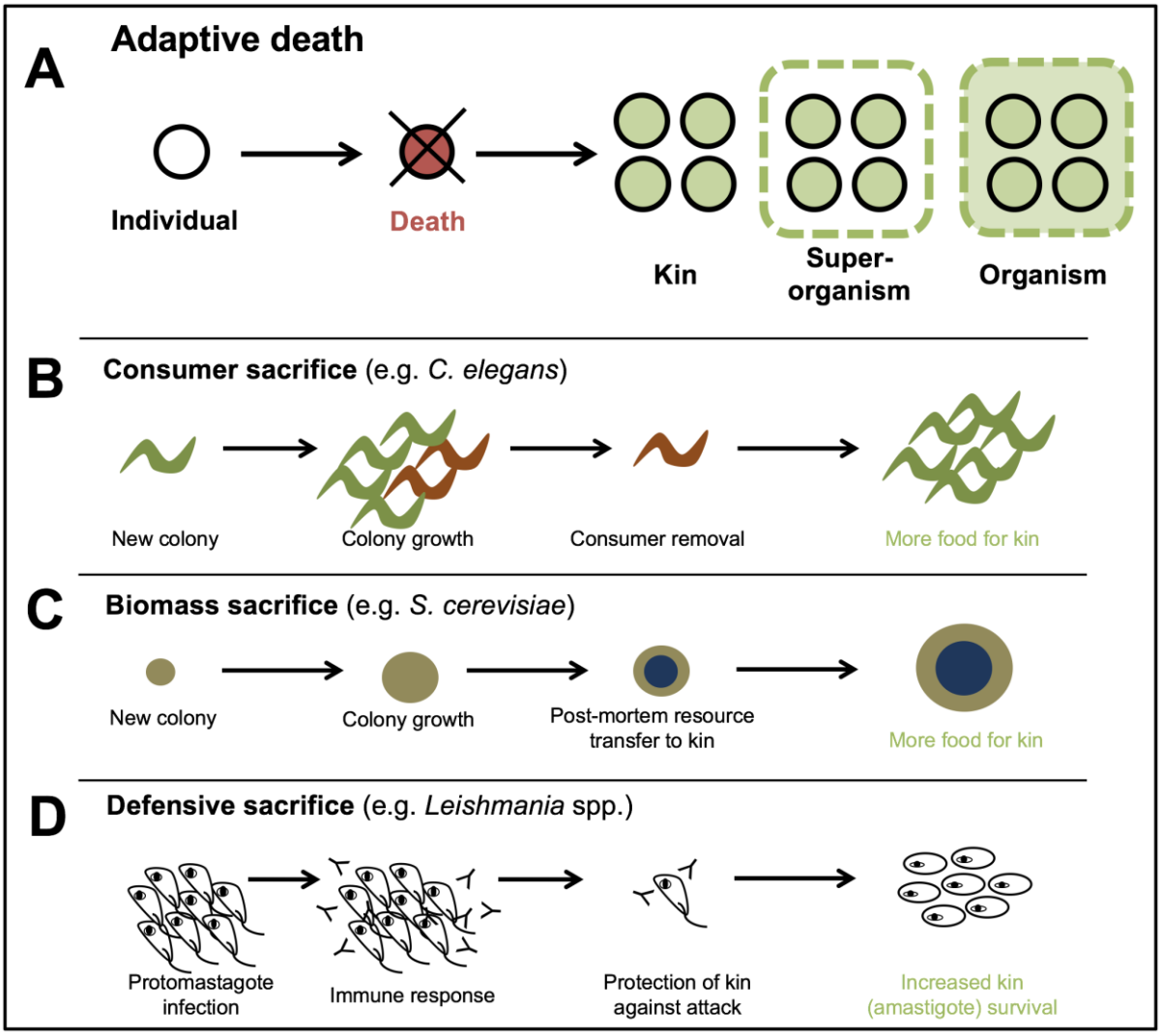

Fig. 1. Adaptive death and forms that it can take. (A) When organisms that can exist as independent individuals associate into social entities with super-organism-like features programmed death can increase inclusive fitness. For death to be adaptive, it must in itself provide a benefit to kin or the (super)-organism, rather than merely being a cost resulting from a beneficial trait. (B) In consumer sacrifice death of older individuals results in fewer mouths to feed, increasing resources for kin. This could, in theory, increase inclusive (or colony level) fitness in *C. elegans* which has a boom and bust lifestyle, and a very short reproductive period (3). (C) Biomass sacrifice occurs when parental individuals or cells die to facilitate transfer of nutrients from their own biomass to kin. In *S. cerevisiae* programmed cell death is thought to promote growth elsewhere in the yeast colony through release of nutrients (35). (D) In defensive sacrifice death increases the chance of kin survival due to enemy attack. A possible example is the protozoan parasite *Leishmania spp.,* where programmed cell death has been suggested to reduce the host immune response against kin (36).