LETTER

REPLY TO GARG AND MARTIN: The mechanism works

István Zachar[a,b,c], András Szilágyi[a,b,c], Szabolcs Számadó[d], and Eörs Szathmáry[a,b,c,1]

Garg and Martin (1) formulate two problems regarding our recent modeling paper (2), demonstrating how prudent predation and farming by a phagotrophic host could lead to endosymbiotic establishment and how they might have had a role in the origin of mitochondria.

We see three main problematic items in Garg and Martin's (1) criticism. These problems concern: (*i*) the issue of phagotrophy without (or before) mitochondria, (*ii*) the question of alternative bet-hedging strategies, and (*iii*) the status of eukaryogenesis as an idiosyncratic megaevolutionary transition. We discuss these concerns in turn.

First, Garg and Martin (1) state that "the physiological benefit of evolving phagocytosis ... is only realized in the presence of mitochondria." This is not so, as the free-living amitochondriate protists testify. These organisms make a living of predation without mitochondria (and hydrogenosomes or mitosomes) (3). The question of whether the evolutionary path needs an energetic boost, allegedly transiently bumping-up the genome size of the evolving lineage to up to a hundred thousand genes (4), is another matter, but this suggestion remains highly controversial (5, 6).

Second, Garg and Martin (1) point out that there are alternative strategies to hedge your bets. This is certainly true: the actual path taken is bound to be historically contingent. Certainly, there are examples in the living world that farming can work, so this idea is as good as any other. More importantly, while glycogen is synthesized by the cell at its energetic and material expense, a reproducing endosymbiont grows autonomously (there is some energetic cost to the host cell due to necessary extra nutrient transport through its membrane). As we write in our paper (2): "If the farm autonomously grows within the host, allocation becomes a neutral trait." Nevertheless, we plan to undertake a directed modeling study of the competitive advantages of the two rival strategies involved.

Third, because of its profound uniqueness, there must have been some idiosyncratic component to eukaryogenesis. Garg and Martin (1) identify this step with the critical endosymbiotic syntrophy (cf. ref. 7); early phagocytosis with the concomitant cellular reorganization (8) is another possible, unique series of events. Martin et al. (9) present numerous arguments against early phagotrophy, but we do not consider any of them decisive; detailed elaboration of this point warrants in-depth examination. Here we just call attention to the fact that a stimulating scenario for the emergence of minimal phagocytosis (10) has escaped Garg and Martin's (1) scrutiny.

All existing consistent scenarios for eukaryogenesis involve difficult ("improbable"), yet possible steps. The jury is out on the question of whether any of them are actual. Furthermore, the mechanism we have modeled (2) might well be a not uncommon factor behind endosymbioses.

1 Garg SG, Martin WF (2018) Asking endosymbionts to do an enzyme's job. *Proc Natl Acad Sci USA*, 10.1073/pnas.1804397115.
2 Zachar I, Szilágyi A, Számadó S, Szathmáry E (2018) Farming the mitochondrial ancestor as a model of endosymbiotic establishment by natural selection. *Proc Natl Acad Sci USA* 115:E1504–E1510.
3 Cavalier-Smith T, Chao EE (1996) Molecular phylogeny of the free-living archezoan *Trepomonas agilis* and the nature of the first eukaryote. *J Mol Evol* 43:551–562.
4 Lane N (2011) Energetics and genetics across the prokaryote-eukaryote divide. *Biol Direct* 6:35.
5 Zachar I, Szathmáry E (2017) Breath-giving cooperation: Critical review of origin of mitochondria hypotheses: Major unanswered questions point to the importance of early ecology. *Biol Direct* 12:19.
6 Szathmáry E (2015) Toward major evolutionary transitions theory 2.0. *Proc Natl Acad Sci USA* 112:10104–10111.
7 de Duve C (2007) The origin of eukaryotes: A reappraisal. *Nat Rev Genet* 8:395–403.

[a]Department of Plant Systematics, Ecology, and Theoretical Biology, Eötvös Loránd University, Budapest 1117, Hungary; [b]Evolutionary Systems Research Group, Centre for Ecological Research, Hungarian Academy of Sciences, Tihany 8237, Hungary; [c]Center for the Conceptual Foundations of Science, Parmenides Foundation, 82049 Pullach/Munich, Germany; and [d]Center for Social Sciences, Hungarian Academy of Sciences "Lendület" Research Center for Educational and Network Studies, 1097 Budapest, Hungary

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[1]To whom correspondence should be addressed. Email: szathmary.eors@gmail.com.

8 Cavalier-Smith T (2014) The neomuran revolution and phagotrophic origin of eukaryotes and cilia in the light of intracellular coevolution and a revised tree of life. *Cold Spring Harb Perspect Biol* 6:a016006.
9 Martin WF, Tielens AGM, Mentel M, Garg SG, Gould SB (2017) The physiology of phagocytosis in the context of mitochondrial origin. *Microbiol Mol Biol Rev* 81:e00008–e00017.
10 Cavalier-Smith T (2009) Predation and eukaryote cell origins: A coevolutionary perspective. *Int J Biochem Cell Biol* 41:307–322.