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The challenge now is to explain how such sensitivity arises.

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# The Bacterivore's Solution: Fight and Flight to Promote Survival

**Yi-Tang Lee[1,2] and Meng C. Wang[1,2,3,4,*]**
[1]Integrative Program in Molecular and Biomedical Sciences, Baylor College of Medicine, Houston, TX 77030, USA
[2]Huffington Center on Aging, Baylor College of Medicine, Houston, TX 77030, USA
[3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA
[4]Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX 77030, USA
*Correspondence: wmeng@bcm.edu
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**Bacterial avoidance and innate immune response are two ways by which *C. elegans* respond to pathogenic bacteria. In this issue of *Developmental Cell*, Kumar et al. (2019) and Singh and Aballay (2019) demonstrate that bacterial colonization is essential to induce both responses, which may be associated with somatic and reproductive longevity.**

While germophobia may be a psychological issue for humans, avoiding pathogenic bacteria is a matter of life and death for *Caenorhabditis elegans*. Upon exposure to certain pathogenic bacteria, worms can die within only hours or days, in contrast to their normal lifespan of 3 weeks (Tan et al., 1999). To avoid this fate, worms may run away, and this protective avoidance behavior can be elicited within minutes (rapid) or hours (late), dependent upon the type of pathogen. In this issue of *Developmental Cell*, findings from Kumar et al. (2019) and Singh and Aballay (2019) reveal that bacterial colonization and consequent

Singh and Aballay (2019) study avoidance behaviors upon exposure to pathogenic bacteria. They discover that with pathogenic *Pseudomonas aeruginosa*, wild-type worms elicit a late avoidance behavior, which is positively correlated with bacterial colonization in the intestine. They further confirm that the inhibition of bacterial colonization abrogates the avoidance response, while the elevation of bacterial colonization caused by defects in either pharyngeal pumping or defecation motor program (DMP) is sufficient to elicit the avoidance response. Interestingly, like the long-lived pharyngeal pumping mutants, the DMP mutants

sion through characterization of a mutant from a forward genetic screen. In a previous genetic screen, the authors identified a loss-of-function mutation in *phm-2*, which extended reproductive span in *C. elegans* (Hughes et al., 2011). They now show that a mutation in *phm-2* causes abnormalities in pharyngeal grinder function and that this mutation extends lifespan. Interestingly, this mutation also leads to increased avoidance behavior and bacterial colonization in the intestine, which are associated with its pro-longevity effects. Together, these two studies suggest that bacterial colonization induces an avoidance behavioral

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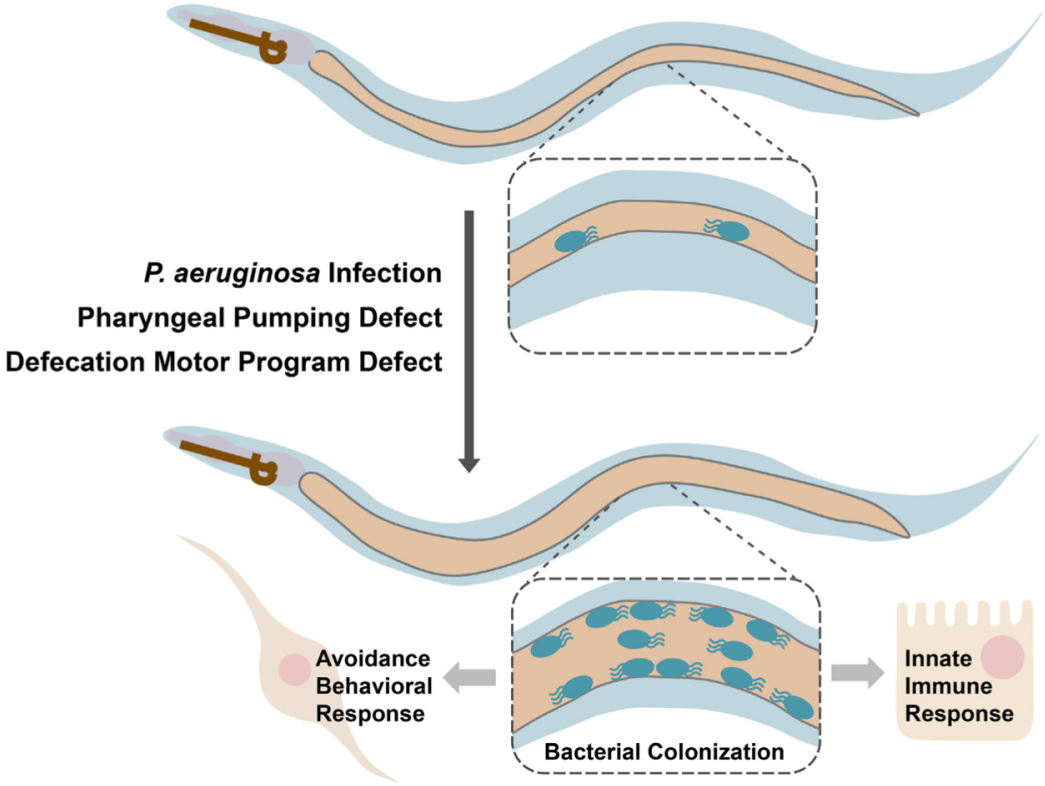


**Figure 1. Intestinal Colonization of Bacteria Promotes Avoidance Behavior and Innate Immune Response**
In *Caenorhabditis elegans*, colonization of bacteria in the intestine can be induced by *Pseudomonas aeruginosa* infection or by defects in the pharyngeal pump or the defecation motor. The increased bacterial colonization promotes avoidance behavior via specific neuronal signals and activates innate immune response gene expression to improve organism survival.

To characterize the underlying molecular mechanisms, the two groups both investigate neuronal mechanisms that are linked to avoidance responses but diverge to different signals. Kumar et al. (2019) confirm that the increased avoidance response caused by the *phm-2* mutation requires TPH-1-mediated serotonin biosynthesis but is independent of NPR-1-mediated neuropeptide signals. On the other hand, Singh and Aballay (2019) reveal that the avoidance caused by increased colonization of *P. aeruginosa* in the DMP mutants requires NPR-1 and the two neuropeptides FLP-18 and FLP-21, but serotonin biosynthesis through TPH-1 plays a negligible role here. It remains unclear what might cause this discrepancy. One possibility is that increased bacterial colonization caused by defective pharyngeal pumping or DMP employs different bacteria may elicit distinct avoidance behaviors.

In addition to the avoidance response, worms protect themselves from bacterial infection by activating the innate immune response (Marsh and May, 2012). Both studies demonstrate that increased intestinal colonization of bacteria transcriptionally induces innate immune response genes. Specifically, Kumar et al. (2019) discover that in the *phm-2* mutant, innate immune response genes are induced with mildly pathogenic *E. coli*, which requires the nuclear accumulation of HLH-30, an ortholog of vertebrate transcription factor EB (TFEB) known to regulate innate immune genes in *C. elegans* (Visvikis et al., 2014). Singh and Aballay (2019) show that innate immune response genes can be upregulated even by heat-killed *E. coli* that cause bloated intestinal lumen. Thus, bacterial colonization induced bloating of in-

although both avoidance behavioral and innate immune responses are elicited by intestinal accumulation of bacteria, their regulatory mechanisms appear to be independent of each other. Kumar et al. (2019) discover that although mutating *hlh-30*/TFEB fully abrogates the induction of innate immune response genes, it has no effect on the avoidance response in the *phm-2* mutant. One possible explanation for this result is that the innate immune response may occur in the intestine cell autonomously, while the avoidance behavioral response is mediated through neurons cell non-autonomously.

Importantly, these two studies also make us reevaluate genetic models of caloric restriction in *C. elegans*. Mutants defective in pharyngeal pumping decrease food intake and have been commonly utilized to study caloric restriction-mediated lifespan extension.

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colonization of bacteria and avoidance behavior. Kumar et al. (2019) further show that the *phm-2* mutation does not enhance the lifespan extension in the *eat-2* mutant and requires *pha-4*, the FOXA transcription factor acting downstream of the *eat-2* mutant, to prolong lifespan. In addition, they show that the *hlh-30* mutation that mediates the induction of innate immune response in the *phm-2* mutant also partially suppresses the lifespan extension. Together with the lifespan extension observed in the DMP mutants that induce innate immune response without pathogen infection, these studies support the idea that the longevity benefit in the pharyngeal defective mutants is not simply a result of reduced food intake, but a combination of bacterial colonization, innate immune activation, bacterial avoidance, and caloric restriction. It has been a long-term mystery why different regimes of caloric restriction in *C. elegans* act through different molecular mechanisms (Greer and Brunet, 2009). These two studies shed light on this question and nicely integrate intestinal recognition of microbes, neural control of behaviors, and longevity responses to dietary intervention.

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