Developmental Cell Previews

The challenge now is to explain how such sensitivity arises.

REFERENCES


The Bacterivore’s Solution: Fight and Flight to Promote Survival

Yi-Tang Lee1,2 and Meng C. Wang1,3,4,*

1Integrative Program in Molecular and Biomedical Sciences, Baylor College of Medicine, Houston, TX 77030, USA
2Huffington Center on Aging, Baylor College of Medicine, Houston, TX 77030, USA
3Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA
4Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX 77030, USA
*Correspondence: wmseng@bcm.edu
https://doi.org/10.1016/j.devcel.2019.03.021

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 bacterial avoidance behaviors occur in the same cell types in germfree worms. This suggests that bacterial avoidance behaviors are a key response to pathogenic bacterial colonization. Kumar et al. (2019) use phm-2 and pmf-1 loss-of-function mutants to study how avoidance behaviors are initiated and suppressed. These genetic mutants do not suppress avoidance behaviors, which is consistent with a role for pmf-1 in regulating the expression of avoidance behavior. 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 also exhibit an increase in mean lifespan 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
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 neuron sets.

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 up-regulated even by heat-killed E. coli that cause bloated intestinal lumen. Thus, bacterial colonization induced bloating of intestinal lumen, 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 hth-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.
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 hlih-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.

REFERENCES