The role of animal pheromones in regulating fat burning and longevity

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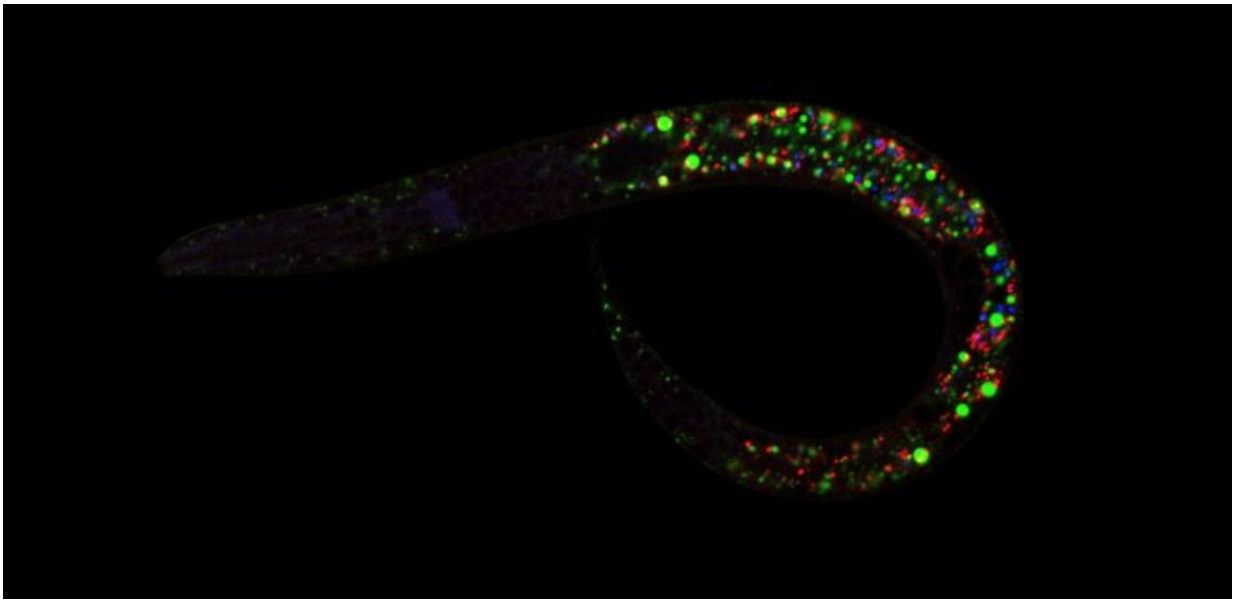


Confocal image of a C. elegans with fat metabolic structures labeled by fluorescent dyes and proteins. Red, fat burning peroxisomes. Green, fat storing lipid droplets. Blue, food digesting lysosomes. Credit: Science China Press , Qi Li.

Pheromones are potent molecules that mediate communications between animals and even between humans. Usually, a sender animal synthesizes and excretes pheromones to the environment; pheromones are detected by a receiver animal and elicit dramatic changes in the development, growth, metabolism, and sex behavior of the receiver animal. In a paper

published in *Science China Life Sciences*, scientists found that in the nematode species C. elegans, pheromones can also be synthesized in the receiver animal and work as hormones inside the receiver animal to regulate fat burning and lifespan.

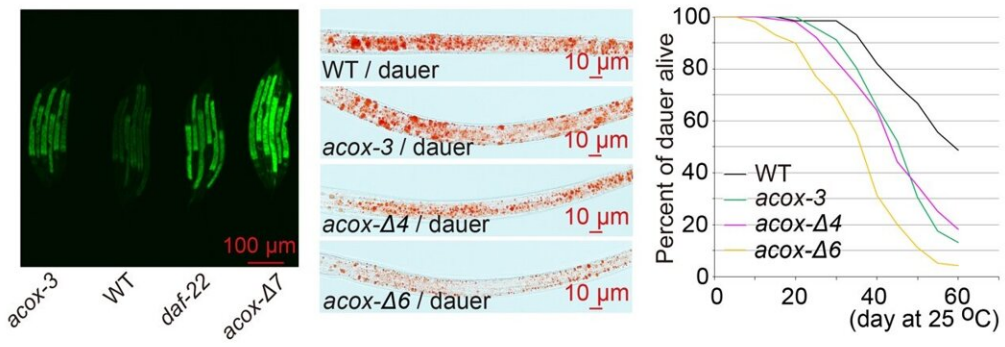
The nematode worm C. elegans synthesizes and excretes pheromones to the habitat. One type of pheromone, dauer pheromones, are detected by olfactory neurons of young receiver larvae in the habitat. When environmental conditions become harsh, e.g., starvation, drought and hot temperature, receiver larvae suspend development and enter an alternative hibernation-like life stage called the dauer larvae.

Dauer larvae can withstand these harsh conditions and live up to four months, much longer than its normal lifespan of 18 days. Dauer formation is an elegant strategy for the worm to survive unfavorable seasons. To survive, dauer larvae must store a sufficient amount of body fat before dauer entry and burn fat slowly during the dauer stage so as to supply a basal level of energy for its survival. This phenomenon is known as fat rationing. How dauer larvae ration body fat has been a mystery. One guess is that dauer pheromones, the very agents that induce dauer formation, are the key. Previously, scientists knew that the receiver larva that sniffs environmental dauer pheromones also synthesizes dauer pheromones and stores a large portion of dauer pheromones in its body. However, the function of internal dauer pheromones has not been studied.

In the current study, Dr. Shaobing O. Zhang and colleagues (College of Life Sciences, Capital Normal University, Beijing) report that it is indeed dauer pheromones that regulate fat rationing and longevity of dauer larvae. Surprisingly, it is not the external environmental pheromones, but the internal body pheromones, that ration fat in the receiver larvae and in the induced dauer larvae.

Previously, Dr. Zhang's group and other groups showed that dauer pheromones are synthesized in a type of organelle called peroxisomes in the worm's gut cells. The chain of chemical reactions in peroxisomes called β-oxidation catalyzes a class of fat-sugar compounds into the final active dauer pheromone molecules. β-oxidation is also the major route for C. elegans to burn fat. "The fact that dauer pheromone synthesis and fat burning are carried out by the same β-oxidation reactions suggests that the two processes are intimately linked. But how? That question has bugged scientists for a long time," said Dr. Zhang.

During the current research, graduate students Cheng Gao and Qi Li discovered that the worm has seven enzymes for the first β-oxidation reaction step but only one of them, ACOX-3, participates in fat burning; the other six, ACOX-1.1 to ACOX-1.6, together with ACOX-3, participate in dauer pheromone synthesis. By selectively deleting the genes encoding the six pheromone-specific ACOX enzymes, the researchers created worms synthesizing different amounts of dauer pheromones. They found that the less pheromones synthesized in the worms, the higher the expression level of the fat-burning-specific ACOX-3 (image below left); hence, fat is burned faster and less fat is stored in the dauer larvae (image below center). Interestingly, during hunger, leaner dauer larvae lives for a much shorter span than fatter dauer larvae (image below right).



On the left, the expression of fat burning enzymes (green) is the lowest in normal larvae (WT), but higher in gene deletion mutant larvae (acox-3) that synthesize less pheromones, and the highest in mutant larvae (acox-Δ7 & daf-22) that synthesize no pheromones. In the center, the pheromone-less acox mutant dauer larvae store less fat than WT (fat storing lipid droplets stained red). On the right, during hunger, the pheromone-less acox mutant dauer larvae live shorter than WT. Credit: ©Science China Press , Cheng Gao and Shaobing O. Zhang.

The researchers found that when they gave pheromones to the receiver worm, the rate of fat burning did not change. However, when they injected pheromones into the body of the receiver worm, fat burning rate decreased. With further experiments, the researchers found that the pheromones inside the receiver worm are sensed by two key HNF4a family nuclear receptors, NHR-79 and NHR-49, to repress the expression of the fat-burning enzymes and a few pheromone synthesis enzymes.

"This finding is counterintuitive. But our data are compelling to reach this conclusion. And it makes all sense," said Dr. Zhang. "When

pheromones are excreted to the environment, the concentration varies a lot according to the volume and diffusion property of the environment; it is difficult for the worm to interpret and respond internally. However, the volume of the worm body is relatively constant, so is the concentration of internal pheromones. This provides a feedback mechanism by which both pheromone synthesis and fat burning are kept low and stable inside the worm, which is beneficial for the long term survival of dauer larvae," Dr. Zhang explained.

The dauer pheromone synthesis enzymes, fat burning enzymes, and HNF4a family nuclear receptors all have counterparts in mammals and in humans. This study points out that these enzymes and factors may ration fat in humans. It also implies that many known pheromones may have inner hormonal functions in the sender or receiver animals that synthesize pheromones.

More information: Cheng Gao et al, Endocrine pheromones couple fat rationing to dauer diapause through HNF4α nuclear receptors, *Science China Life Sciences* (2021). DOI: 10.1007/s11427-021-2016-9

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