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Making skinny worms fat, fat worms skinny

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The UCSF team identifed chemical compounds that reduced the accumulation of fat (highlighted in red) in worms, as seen in the treated worms. Credit: Kaveh Ashrafi/UCSF

(PhysOrg.com) -- Researchers exploring human metabolism at the University of California, San Francisco (UCSF) have uncovered a handful of chemical compounds that regulate fat storage in worms, offering a new tool for understanding obesity and finding future treatments for diseases associated with obesity.

As described in a paper published this month in the journal *Nature Chemical Biology*, the UCSF team took armies of microscopic worms called C.elegans and exposed them to thousands of different chemical compounds. Giving these compounds to the worms, they discovered, basically made them skinnier or fatter without affecting how they eat, grow, or reproduce.

The discovery gives scientists new ways to investigate metabolism and could eventually lead to the development of new drugs to regulate excessive fat accumulation and address the metabolic issues that underlie a number of major human health problems, including, obesity, diabetes and some forms of cancer.

The work also demonstrates the value of “worm screening” as a way of finding new targets for human diseases, according to the UCSF scientists, whose work was spearheaded by postdoctoral fellow George Lemieux, PhD, in the laboratory of Professor Zena Werb, PhD, vice chair of the Department of Anatomy at UCSF.

The work was a collaboration involving Kaveh Ashrafi, PhD, an associate professor in the UCSF Department of Physiology, and Roland Bainton, MD, PhD, an associate professor in residence in the UCSF Department of Anesthesia & Perioperative Care.

Why Worms Are Fat

The UCSF team’s interest in how worms deal with fat began with a more fundamental interest in human metabolism. Worms make molecules of fat for the same reasons humans do – they are useful for storing energy and are a basic building block for body tissues. Many of the genes and mechanisms worms use to regulate fat accumulation have similar systems in humans, and not all of them are completely understood.

Starting with 3,200 different chemical compounds and 3,200 pools of tiny worms, the UCSF team used a red dye that sticks to fat molecules to pinpoint under the microscope which of the chemicals made the worms fatter (more red) or skinnier (less red). They identified a few dozen, and performing additional tests, narrowed in on about 10 compounds they believe regulate fat metabolism. Those compounds not only altered fat storage in the worms but in in insect and human cells grown in test tubes, leading Lemieux to comment that they “may be useful for understanding metabolism in other organisms.”

One of these compounds modulates a molecular complex called an AMP-activated kinase, which senses the availability of cellular energy. Versions of kinase complexes exist both in worms and humans, and some already are key targets for drug design by pharmaceutical companies.

“The compound that we get from our worm screen can act on this kinase complex as well if not better than anything else that is out there,” said Ashrafi.

The real strength of the work, he added, is that it demonstrates the value of the new worm screen over existing screening tools for identifying the genes, proteins and other molecular players involved in human health.

A large part of drug discovery involves identifying these players and designing ways to treat diseases that emerge when they don’t work correctly. But identifying the targets is only the beginning. Designing a drug involves overcoming a long list of other hurdles, Ashrafi said, and the bottom line is that most of the potential drugs that seem to work well in the test tube fail to work in people.

The value of the worm screen, he said, is that it allows scientists to select compounds for further study that already work effectively in a whole organism.

“A lot of the drugs that are in clinical use or development today were discovered basically by chance,” Ashrafi said. “If we understood everything about everything, we could probably design the right compounds. But the reality is our understanding of many of the biological principles and chemical principles are still in their infancy.”

More information: dx.doi.org/10.1038/nchembio.534

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