RNA molecule behind behavior changes cued by environment

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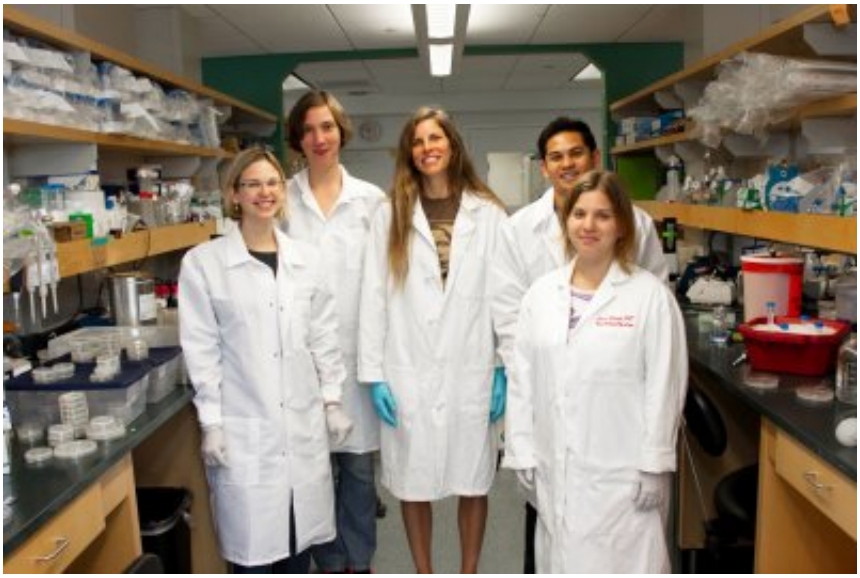

The L'Etoile Lab in the Department of Cell and Tissue Biology, from left: Mary Bethke,lab manager; Chantal Brueggemann, PhD, postdoctoral scholar; Noelle L'Etoile, PhD;Adriel-John Ablaza, staff research associate; and Katherine Mellman, graduate student.

Quick changes in behavior – in worms, at least – can be triggered by a unique form of the molecule RNA acting within the nucleus of a cell, UC San Francisco researchers have discovered.

The finding adds to mounting evidence for the importance of RNA in controlling gene activity, for its likely role in disease and for its potential

as a therapeutic target.

Recognition of RNA's importance has led the National Institutes of Health and other research organizations to fund more research directed toward better understanding the molecule's role in disease and its therapeutic potential.

In a study published online on Aug. 29 in the journal *Cell*, scientists led by UCSF's Noelle L'Etoile, PhD, found that the nerve cells of the tiny nematode worm C. elegans quickly learn to stop following a scent and eventually ignore it after an odor fails to lead the worm to food.

The researchers speculate that a similar biological mechanism involving RNA might drive long-lasting physiological changes in many types of human cells as they adapt to changes in the surrounding environment. "Our work indicates a mechanism by which environmentally relevant experiences may regulate gene expression, thereby shaping behavior in a specific and dynamic fashion," said L'Etoile, an associate professor in the UCSF School of Dentistry's Department of Cell & Tissue Biology.

Therapeutic possibilities with RNA interference

The behavior change is a consequence of a negative feedback triggered inside a nerve cell, the researchers determined.

The particular form of RNA responsible for the rapid behavior change is called endogenous, small interfering RNA (endo siRNA), and until now, nobody had described a dynamic physiological role for it, let alone one that regulates behaviors, according to L'Etoile. So far, endo siRNA has been identified in yeast, worms and fruit flies, but not yet in mammals such as humans.

Endo siRNA is one a several types of short RNA molecules that

researchers have discovered engage in "RNA interference." Although it was not discovered until the late 1990s, nearly 40 years after the genetic code for making proteins from genes was identified, the phenomenon of RNA interference now is known to play an important role in fighting viral infection and in preventing genetic mayhem during reproduction by preventing parts of the genome known as "jumping genes" from moving and disrupting DNA within stable, vital genes.

Scientists' growing understanding of the scope of RNA interference has inspired new experimental strategies for manipulating gene activity therapeutically.

Worm nerve cells are a window on basic biology

Over the past two decades, UCSF researchers – including former UCSF faculty member Cori Bargmann, PhD, now at Rockefeller University – have used the worm as a model for exploring the underlying basis of behaviors.

Among other discoveries, Bargmann found four nerve cells that the worm uses to detect odors in the environment and to track down its favorite food: tasty bacteria. She also found hundreds of odor receptor proteins that the worm uses to detect specific scents.

A decade ago, as a post-doctoral fellow in Bargmann's lab, L'Etoile cloned a gene for a protein called odr-1, needed for odor recognition.

In the newly published *Cell* study, the researchers probed how just one nerve cell in the worm responds to the scent of butanone, one of the chemicals that can signal the location of bacteria. Bargmann had earlier discovered that when worms are presented with butanone absent any bacteria, they adapt within an hour and stop gravitating toward the source of the chemical. "This change in behavior indicated a memory

formation, and we wanted to know the molecular basis of this," L'Etoile said.

Endo siRNA remains one of the least understood agents of RNA interference, according to L'Etoile.

It is made from a gene's specific messenger RNA, the sequence of nucleic acid building blocks that carries the genetic blueprint of a protein to the cell's protein-making machinery outside the nucleus. As a consequence, endo siRNA specifically targets only that gene, L'Etoile said, unlike other types of RNAs involved in RNA interference. Endo siRNA also acts a step earlier to block gene activity, by getting into the cell's nucleus and stopping the formation of new messenger RNA, rather than simply by destroying existing messenger RNA in the cell's cytoplasm.

Endo siRNA specific for the odr-1 gene stops the gene from making the messenger RNA, the researchers found in their new study. L'Etoile's collaborator, Scott Kennedy, PhD, of the University of Wisconsin, Madison, determined how endo siRNA can ride on specific proteins to get into the nucleus where it can act to turn off genes. Bi-Tzen Juang, PhD, a postdoctoral fellow in L'Etoile's lab, conducted experiments showing that a protein called EGL-4, acting downstream from odr-1, also is needed for the worm to adapt to the unrewarding butanone signal.

"This mechanism allows an environmental stimulus to potentially dial down the activity of any gene," L'Etoile said. "Thus any gene may sow the seeds of its own inactivation under the right circumstances."

More information: www.sciencedirect.com/science/ … ii/S009286741300963X