Acquired traits can be inherited via small RNAs

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Columbia University Medical Center (CUMC) researchers have found the first direct evidence that an acquired trait can be inherited without any DNA involvement. The findings suggest that Lamarck, whose theory of evolution was eclipsed by Darwin's, may not have been entirely wrong. The study is slated to appear in the December 9 issue of *Cell*.

"In our study, roundworms that developed resistance to a virus were able to pass along that immunity to their progeny for many consecutive generations," reported lead author Oded Rechavi, PhD, associate research scientist in biochemistry and molecular biophysics at CUMC. "The immunity was transferred in the form of small viral-silencing agents called viRNAs, working independently of the organism's genome."

In an early theory of evolution, Jean Baptiste Larmarck (1744-1829) proposed that species evolve when individuals adapt to their environment and transmit those acquired traits to their offspring. For example, giraffes developed elongated long necks as they stretched to feed on the leaves of high trees, an acquired advantage that was inherited by subsequent generations. In contrast, Charles Darwin (1809-1882) later theorized that random mutations that offer an organism a competitive advantage drive a species' evolution. In the case of the giraffe, individuals that happened to have slightly longer necks had a better chance of securing food and thus were able to have more offspring. The subsequent discovery of hereditary genetics supported Darwin's theory, and Lamarck's ideas faded into obscurity.

However, some evidence suggests that acquired traits can be inherited. "The classic example is the Dutch famine of World War II," said Dr. Rechavi. "Starving mothers who gave birth during the famine had children who were more susceptible to obesity and other metabolic disorders — and so were their grandchildren." Controlled experiments have shown similar results, including a recent study in rats demonstrating that chronic high-fat diets in fathers result in obesity in their female offspring.

Nevertheless, Lamarckian inheritance has remained controversial, and no one has been able to describe a plausible biological mechanism, according to study leader Oliver Hobert, PhD, professor of biochemistry and molecular biophysics and a Howard Hughes Medical Institute Investigator at CUMC.

Dr. Hobert suspected that RNA interference (RNAi) might be involved in the inheritance of acquired traits. RNAi is a natural process that cells use to turn down, or silence, specific genes. It is commonly employed by organisms to fend off viruses and other genomic parasites. RNAi works by destroying mRNA, the molecular messengers that carry information coded in a gene to the cell's protein-making machinery. Without its mRNA, a gene is essentially inactive.

RNAi is triggered by doubled-stranded RNA (dsRNA), which is not found in healthy cells. When dsRNA molecules (for example, from a virus) enter a cell, they are sliced into small fragments, which guide the cell's RNAi machinery to find mRNAs that match the genetic sequence of the fragments. The machinery then degrades these mRNAs, in effect destroying their messages and silencing the corresponding gene.

RNAi can be also triggered artificially by administering exogenous (externally derived) dsRNA. Intriguingly, the resultant gene-silencing occurs not only in the treated animal, but also in its offspring. However, it was not clear whether this effect is due to the inheritance of RNAs or to changes in the organism's genome — or whether this effect has any biological relevance.

To look further into these phenomena, the CUMC researchers turned to the roundworm (*C. elegans*). The roundworm has an unusual ability to fight viruses, which it does using RNAi.

In the current study, the researchers infected roundworms with Flock House virus (the only virus known to infect *C. elegans*) and then bred the worms in such a way that some of their progeny had nonfunctional RNAi machinery. When those progeny were exposed to the virus, they were still able to defend themselves. "We followed the worms for more than one hundred generations — close to a year — and the effect still persisted," said Dr. Rechavi.

The experiments were designed so that the worms could not have acquired viral resistance through genetic mutations. The researchers concluded that the ability to fend off the virus was "memorized" in the form of small viral RNA molecules, which were then passed to subsequent generations in somatic cells, not exclusively along the germ line.

According to the CUMC researchers, Lamarckian inheritance may provide adaptive advantages to an animal. "Sometimes, it is beneficial for an organism to not have a gene expressed," explained Dr. Hobert. "The classic, Darwinian way this occurs is through a mutation, so that the gene is silenced either in every cell or in specific cell types in subsequent generations. While this is obviously happening a lot, one can envision scenarios in which it may be more advantageous for an organism to hold onto that gene and pass on the ability to silence the gene only when challenged with a specific threat. Our study demonstrates that this can be done in a completely new way: through the transmission of extrachromosomal information. The beauty of this approach is that it's reversible."

Any therapeutic implications of the findings are a long way off, Dr. Rechavi added. "The basic components of the RNAi machinery exist throughout the animal kingdom, including humans. Worms have an extra component, giving them a much stronger RNAi response. Theoretically, if that component could be incorporated in humans, then maybe we could improve our immunity and even our children's immunity."

The CUMC team is currently examining whether other traits are also inherited through small RNAs. "In one experiment, we are going to replicate the Dutch famine in a Petri dish," said Dr. Rechavi. "We are going to starve the worms and see whether, as a result of starvation, we see small RNAs being generated and passed to the next generation."

The CUMC team's paper is entitled, "Transgenerational inheritance of an acquired small RNA-based antiviral response in *C. elegans*." The other co-author is Gregory Minevich at CUMC.

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