Propensity for longer life span inherited non-genetically over generations, study says

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We know that our environment -- what we eat, the toxic compounds we are exposed to -- can positively or negatively impact our life span. But could it also affect the longevity of our descendants, who may live under very different conditions? Recent research from the Stanford University School of Medicine suggests this could be the case.

Blocking or modifying the expression of any of three key proteins in a laboratory roundworm increases the life span of not only the original animal, but also that animal's descendants, the researchers found. This occurs even though the original modification is no longer present in the descendants. The finding is the first to show that longevity can be inherited in a non-genetic manner over several generations.

It's tempting to translate the findings to humans, who share similar proteins with those studied in the worms in this work. While much more investigation is needed, the research at least hints at the possibility that modifications that occurred in your great-grandparents, perhaps as a result of diet or other environmental conditions, will affect your own life span.

"In some ways, this work relates to the idea of inheritance of acquired traits, which is almost heretical because it has long been discounted by the laws of Mendel," said associate professor of genetics Anne Brunet, PhD. "But we show in this study that the transgenerational inheritance of longevity does occur in roundworms via modulations of proteins that normally add epigenetic modifications to chromatin."

Brunet is the senior author of the study, to be published online Oct. 19 in *Nature*. Former graduate student Eric Greer (now a postdoctoral scholar at Harvard Medical School) is the first author.

The term epigenetics describes a process by which organisms modulate their gene expression in response to environmental cues without changing the underlying sequence of their DNA. Chromatin, the tightly coiled complex of DNA and proteins called histones that keeps the genetic material firmly packed in the cells' nucleus, can be modified in an epigenetic manner by addition or removal of chemical tags on histones or DNA itself. Although most chromatin modifications are reset between generations during the process of reproduction, this study suggests that such reprogramming is incomplete in some cases.

The current research builds on a previous study from Brunet's laboratory that showed that mutations in several chromatin regulators can increase the life span of a laboratory roundworm known as Caenorhabditis elegans by as much as 30 percent. Interestingly, these chromatin regulators control life span by functioning at least in part in the worm's reproductive system, or germ line. That research was published in Nature last year.

Greer and Brunet wondered whether the effect on life span of these chromatin regulators would be conveyed to the worms' descendants, even when the mutations were no longer present. To answer this question, Greer individually mutated each of the genes encoding three proteins — ASH-2, WDR-5 and SET-2 —involved in the chromatin regulatory complex that adds methyl groups to a specific histone in chromatin. The methyl groups work to lock chromatin in an open configuration that is accessible for gene expression.

Greer then bred the worms in such a way that their descendants would no longer have the mutations. He found that the descendants with normal

levels of expression of these three proteins (but with ancestors that were deficient for them) still lived longer than descendants from un-mutated ancestors. This longer life span persisted, in some cases for up to three generations, but did eventually disappear and the worms reverted to a normal life span. When he compared the gene expression profiles of long-lived descendants of mutant ancestors with those of control worms, Greer found several hundred genes whose changes in expression were also inherited.

"We still don't know the exact mechanism of this epigenetic memory of longevity between generations," said Brunet. "We hypothesize that when the parental generation is missing key components that normally regulate chromatin, epigenetic marks are not completely reset from one generation to the next in the germ line, thereby inducing heritable changes in gene expression. It will be very interesting to understand how this happens.

"We are also curious as to whether environmental factors that can affect longevity, like calorie restriction, could also affect subsequent generations," she said.

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