Stress on mothers can influence biology of future generations

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Caenorhabditis elegans. Credit: Wikipedia

A mother's response to stress can even influence her grandchildren.

Biologists at the University of Iowa found that roundworm mothers

subjected to heat stress passed, under certain conditions and through modifications to their genes, the legacy of that stress exposure not only to their offspring but even to their offspring's children.

The researchers, led by Veena Prahlad, associate professor in the Department of Biology and the Aging Mind and Brain Initiative, looked at how a mother roundworm reacts when she senses danger, such as a change in temperature, which can be harmful or even fatal to the animal. In a study published last year, the biologists discovered the mother roundworm releases serotonin when she senses danger. The serotonin travels from her central nervous system to warn her unfertilized eggs, where the warning is stored, so to speak, and then passed to offspring after conception.

Examples of such genetic cascades abound, even in humans. Studies have shown that pregnant women affected by famine in the Netherlands from 1944 to 1945, known as the Dutch Hunger Winter, gave birth to children who were influenced by that episode as adults—with higher rates than average of obesity, diabetes, and schizophrenia.

In this study, the biologists wanted to find out how the memory of stress exposure was stored in the egg cell.

"Genes have 'memories' of past environmental conditions that, in turn, affect their expression even after these conditions have changed," Prahlad explains. "How this 'memory' is established and how it persists past fertilization, embryogenesis, and after the embryo develops into adults is not clear. "This is because during embryogenesis, most organisms typically reset any changes that have been made to genes because of the genes' past activity."

Prahlad and her teams turned to the roundworm, a creature regularly studied by scientists, for clues. They exposed mother roundworms to

unexpected stresses and found the stress memory was ingrained in the mother's eggs through the actions of a protein called the heat shock transcription factor, or HSF1. The HSF1 protein is present in all plants and animals and is activated by changes in temperature, salinity, and other stressors.

The team found that HSF1 recruits another protein, an enzyme called a histone 3 lysine 9 (H3K9) methyltransferase. The latter normally acts during embryogenesis to silence genes and erase the memory of their prior activity.

However, Prahald's team observed something else entirely.

"We found that HSF1 collaborates with the mechanisms that normally act to 'reset' the memory of gene expression during embryogenesis to, instead, establish this stress memory," Prahlad says.

One of these newly silenced genes encodes the insulin receptor, which is central to metabolic changes with diabetes in humans, and which, when silenced, alters an animal's physiology, metabolism, and stress resilience. Because these silencing marks persisted in offspring, their stress-response strategy was switched from one that depended on the ability to be highly responsive to stress, to relying instead on mechanisms that decreased stress responsiveness but provided long-term protection from stressful environments.

"What we found all the more remarkable was that if the mother was exposed to stress for a short period of time, only progeny that developed from her germ cells that were subjected to this stress in utero had this memory," Prahlad says. "The progeny of these progeny (the mother's grandchildren) had lost this memory. However, if the mother was subjected to a longer period of stress, the grandchildren generation retained this memory. Somehow the 'dose' of maternal stress exposure is

recorded in the population."

The researchers plan to investigate these changes further. HSF1 is not only required for stress resistance but also increased levels of both HSF1 and the silencing mark are associated with cancer and metastasis. Because HSF1 exists in many organisms, its newly discovered interaction with H3K9 methyltransferase to drive gene silencing is likely to have larger repercussions.

The paper, "Gene bookmarking by the heat-shock transcription factor programs the insulin-like signaling pathway," was published online Oct. 13 in the journal *Molecular Cell*.

More information: Gene bookmarking by the heat-shock transcription factor programs the insulin-like signaling pathway, *Molecular Cell* (2021).

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