Protein alteration controls cell's response to stress, immunity and lifespan

15 January 2019

Scientists have revealed a key mechanism in worms that is involved in controlling the cell's response to stress, a study in *eLife* reports.

The discovery provides crucial new insights into a stress-response mechanism called unfolded protein response (UPR) and will help researchers understand the processes that protect cells, boost immunity and extend lifespan.

The ability of an organism to cope with an ever-changing and challenging environment lies in its ability to activate stress responses. One of the most important biological components affected by stress are the mitochondria—the energy-producing machinery of our cells. Animals respond to mitochondrial stress by activating the UPR—a surveillance program that monitors mitochondrial function and signals to the nucleus (the control centre of the cell) - if something is wrong. Although some components of the UPR have been identified, exactly how it is controlled is still unclear.

"We had previously identified genes that are important for the activation of the mitochondrial stress response," explains lead author Kaiyu Gao, graduate student at the Institute of Molecular Medicine, Peking University, China. "Among these was the ulp-4 gene, which is an enzyme that removes a molecule called SUMO from proteins, dramatically affecting their function. In this study, we set out to see whether the ULP-4 enzyme was necessary for the stress response, and whether it influenced this response by removing SUMO groups."

The team first blocked the activity of the ulp-4 gene in worms and looked at whether this affected the UPR response. This prevented the stress response in mitochondria but not stress responses in other parts of the cell. When they restored high levels of the ULP-4 molecule into the previously ULP-4-deficient worms, they found the animals were able to activate the mitochondrial stress response, suggesting that ULP-4 is necessary for UPR.

They next looked at how ULP-4 influences the mitochondrial UPR. By conducting protein-binding experiments in yeast cells, they identified two molecules that interact with ULP-4 called DVE-1 and ATFS-1. Both molecules had specific sites where a SUMO group could be added, so the next question was whether ULP-4 was involved in removing these groups, and whether this affected the UPR. The team found that ULP-4 removes the SUMO group from DVE-1. They also revealed that this happens in worms, and with the other molecule that interacts with ULP-4, ATFS-1.

Finally, the researchers looked at how ULP-4 affects the resilience and lifespan of the worms. They found that worms lacking ULP-4 had a suppressed immune response and impaired survival following infection with Pseudomonas bacteria. And under stressed conditions, a deficiency in ULP-4 (or preventing the addition of SUMO groups by mutating DVE-1 or ATFS-1) dramatically reduced lifespan.

"We have identified protein modification that promotes immune response and lifespan extension during mitochondrial stress," concludes senior author Ying Liu, Assistant Professor at the Institute of Molecular Medicine, Peking University. "Whether the addition of SUMO groups affects other proteins in the mitochondrial quality-control process is worthy of exploration. As UPR and ULP-4 exist in humans, targeting SUMO activity could one day be investigated as a potential treatment strategy for mitochondrial disorders and age-related diseases."

More information: Kaiyu Gao et al, SUMO peptidase ULP-4 regulates mitochondrial UPR-mediated innate immunity and lifespan extension, *eLife* (2019). DOI: 10.7554/eLife.41792

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