Unexpected proteome plasticity in response to persistent temperature rise

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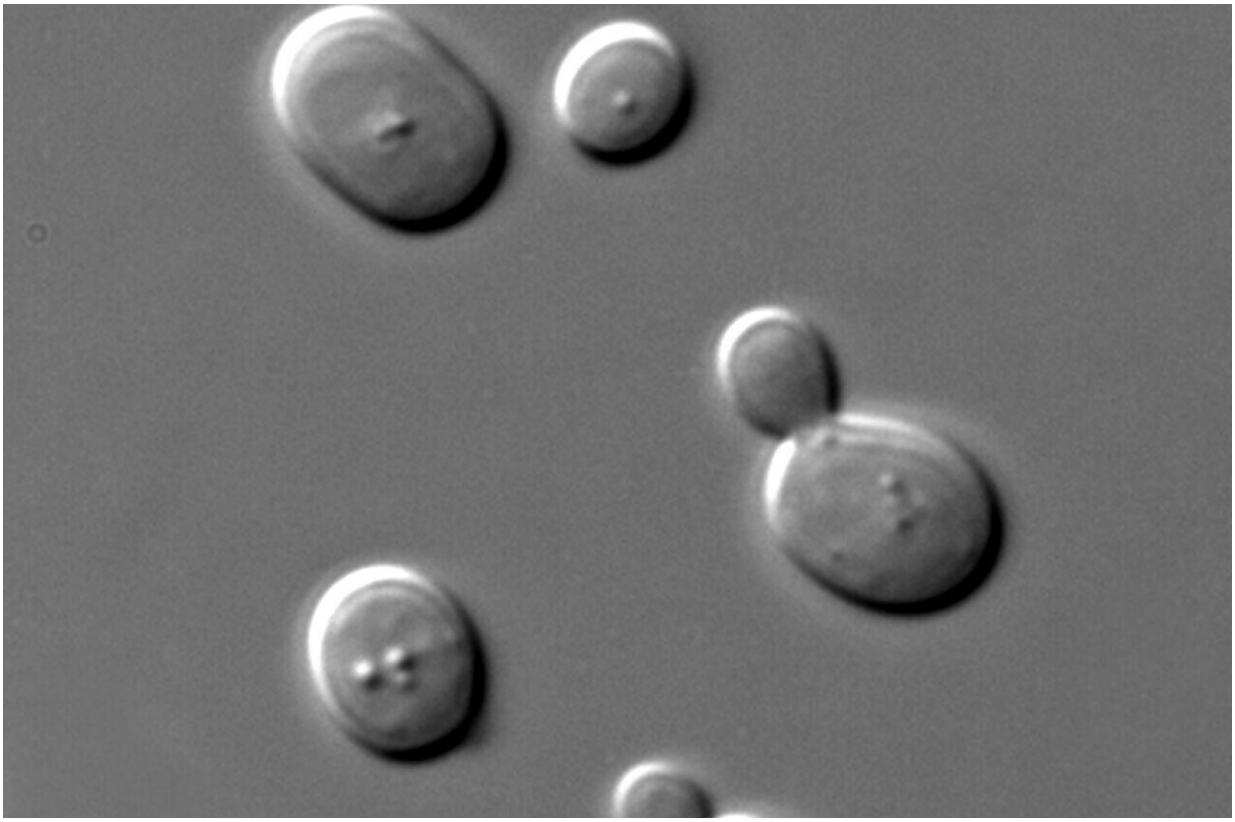

Saccharomyces cerevisiae cells in DIC microscopy. Credit: Public Domain

Common yeast are able to adapt and thrive in response to a long-term rise in temperature by changing the shape, location and function of some of their proteins. The surprising findings demonstrate the unappreciated

plasticity in the molecular and conformational level of proteins and bring the power of molecular biology to the organismal response to climate change. Results from the Zhou lab at the Buck Institute in collaboration with the Si lab from the Stowers Institute are published in *Molecular Cell*.

Temperature is an unstable parameter in the wild, affecting almost all aspects of life by modifying protein stability and the speed of metabolism. Buck Institute Fellow Chuankai "Kai" Zhou, Ph.D., lead scientist of the study, says previous research provides extensive knowledge on how acute, short-term increases in temperature misfolds proteins, revealing how cells respond to such challenges by upregulating molecular chaperones and other stress response proteins to refold/degrade these misfolded proteins in order to help unprepared cells survive sudden changes in their environment. However, Zhou says it is largely unknown whether the cells will continue this misfolding-refolding/degradation cycle of proteins when temperature increase becomes a long-term challenge.

"This is a critical question as climate change and global warming pose a temperature increase that will span generations for most of the species currently living on earth," he said. "Understanding how and whether the organisms are prepared for such long-term global warming at the molecular level is critical in order for us to address the future of our ecosystem."

In this study, Buck researchers followed and compared yeast cultured at room temperature to cells grown at 95 degrees Fahrenheit (35 degrees Celsius) for more than 15 generations. The higher temperature initially resulted in the well-documented stress response seen with short-term temperature rise (or heat shock) including protein aggregation and an increased expression of protective chaperones. After the yeast grew at high temperature for a few generations researchers saw the cells

recuperate and their growth rate gradually accelerate. After 15 generations, protein aggregates disappeared, and many acute stress regulators returned to baseline expression levels. Whole genome sequencing found no genetic mutations. Zhou says somehow the yeast adapted to the temperature challenge.

Using unbiased imaging screening and machine-learning-based image analysis, scientists analyzed millions of cells for the entire yeast proteome and found hundreds of proteins that changed their expression patterns, including abundance and subcellular localizations, after the cells adapted to the higher temperatures. "Interestingly, the proteins that tend to be misfolded by acute stress reduced their expression after the yeast acclimated to the new environment," said Zhou. "This suggests that a possible strategy to avoid the misfolding/refolding cycle under persistent temperature challenge would involve reducing the load of thermolabile proteins." Zhou says subcellular localization is a determinant of protein function. The proteins change their subcellular distribution under persistent shift in temperature to either protect themselves from thermal instability or to perform new functions as a compensation for the reduction of other thermolabile proteins, or both.

"The most exciting and unexpected changes happen at the sub-molecular level of the proteins," said Zhou, "Once the yeast 'realized' the heat stress was long term they changed a lot. Some of their proteins changed conformation (shape). The current paradigm of gene-protein function research has been built on the belief that a protein has ONE final structure. We show that's not the case, for at least some of the proteins that responded to the temperature change."

This discovery comes from a novel proteomics-structural screening pipeline developed by Zhou and colleagues that allowed them to identify many proteins that adopted an alternative shape or conformation after the yeast acclimated to their new environment. Importantly, these

changes in protein conformation were not caused by genetic mutations and most of them did not result in post-translational modifications either. Using Fet3p, a multicopper-containing glycoprotein, as an example, the researchers found that the protein changed location over the generations, moving from the endoplasmic reticulum to the cell membrane during thermal acclimation. "What's most astonishing is that the protein conformation is different as well. It also changes its interacting proteins," said Zhou.

By checking protein-protein interactions and the associated molecular functions, the researchers found that Fet3p, produced at different temperatures, has distinct functions in different cellular compartments. Zhou says the thermal acclimation changed the protein folding and function, allowing one polypeptide to adopt multiple structures and moonlight functions according to the growth environment. "These results together show the plasticity of the proteome and reveal previous unknown strategies available to organisms facing long-term temperature challenges. For simple organism like yeast, which has very limited alternative splicing, such proteome plasticity, or alternative folding of proteins induced by environmental conditions, allows this organism to survive an amazingly broad range of harsh habitats."

While excited about discovering an evolutionary-encoded strategy that allows the yeast to adapt to different temperatures, Zhou points out that resilience cannot be assumed. "We know there is a limit to plasticity—above a certain temperature the yeast will die. Our hope is that this work will enable efforts to learn from Mother Nature about how organisms adapt to climate changes by implementing the encoded plasticity of their proteins. Some species have been through multiple runs of climate changes in the Earth's history and their genomes/proteomes may have learned how to endure such changes. At the same time, many species are new to climate changes and they are most likely at risk of extinction from this current global warming. We

are happy to contribute to urgent questions at the molecular level and welcome collaborations."

Zhou will keep digging into the molecular detail of what changes inside cells during long-term temperature change and plans on including simple animals in his exploration of protein plasticity. He will also study the impact temperature change has on aging.

More information: Proteome plasticity in response to persistent environmental change, *Molecular Cell* (2021). DOI: 10.1016/j.molcel.2021.06.028

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