

Scientists identify the master regulator of cells' heat shock response

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Heat shock proteins protect the molecules in all human and animal cells with factors that regulate their production and work as thermostats. In new research published Sept. 16 in the journal *eLife*, scientists at NYU Langone Medical Center and elsewhere report for the first time that a protein called translation elongation factor eEF1A1 orchestrates the entire process of the heat shock response. By doing so, eEF1A1 supports overall protein homeostasis inside the cell, ensuring that it functions properly under various internal and external stress conditions. The researchers suggest that this finding could reveal a promising, new drug target for neurodegenerative diseases and cancer.

Researchers say a variety of age-related diseases thrive, depending on how cells respond to heat and other types of stress. Heat shock proteins (HSPs) chaperone other proteins, helping them to fold properly and supporting their function. With [neurodegenerative diseases](#), neurons lack enough protective HSPs that insulate them from protein-damaging stress. A hallmark of most neurodegenerative diseases is protein misfolding. If the heat shock response could be restored to its full capacity in aging neurons, then misfolded proteins might fold properly, potentially avoiding or halting progression of diseases such as Alzheimer's, Parkinson's, or amyotrophic lateral sclerosis (ALS). In contrast, many types of [cancer cells](#) rely on HSPs to survive. Because high levels of HSPs enable cancer cells to grow and proliferate, depleting these cells of HSPs could sensitize tumors to chemotherapy and radiation therapies.

"It's a bit early, but we think that eventually we could design small-

molecule activators and inhibitors that tweak the heat shock response," says Evgeny Nudler, PhD, the study's senior investigator and the Julie Wilson Anderson Professor of Biochemistry and Molecular Pharmacology at NYU Langone. "eEF1A1 controls every single step of the heat shock response simultaneously."

Nudler, a Howard Hughes Medical Institute investigator, says his team's latest research shows that eEF1A1 activates transcription by recruiting a key transcription factor to heat shock genes. It also stabilizes HSP mRNAs and helps to transport these RNAs outside the cell nucleus and delivers them to the cell's ribosome for [protein synthesis](#). In this way, Nudler says, it orchestrates the entire process of manufacturing HSPs in response to stress. HSPs then bind to other proteins, preventing their toxic aggregation.

The eEF1A protein is expressed in two similar forms, 1 and 2, in different tissues. Nudler and colleagues show, for example, that motor neurons express form 2 (eEF1A2), which does not support the heat shock response. They believe that this is the reason why these specialized [cells](#) cannot mount the heat shock response and therefore are particularly vulnerable to stress and diseases such as ALS. The challenge in drug development will be restoring the [heat shock](#) response in [motor neurons](#) by modulating the activity of eEF1A.

Nudler's laboratory used various human and mouse cell lines in this work. Maria Vera, PhD, a former member of Nudler's laboratory, was the lead study investigator. Other key study participants include Bibhusita Pani, PhD, also from Nudler's lab; Robert Singer, PhD, from Albert Einstein College of Medicine in Bronx, NY; and Cathy Abbott, PhD, from the University of Edinburgh in Scotland.

Provided by New York University School of Medicine

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