Team identifies new mechanism for misfolded proteins in heart disease

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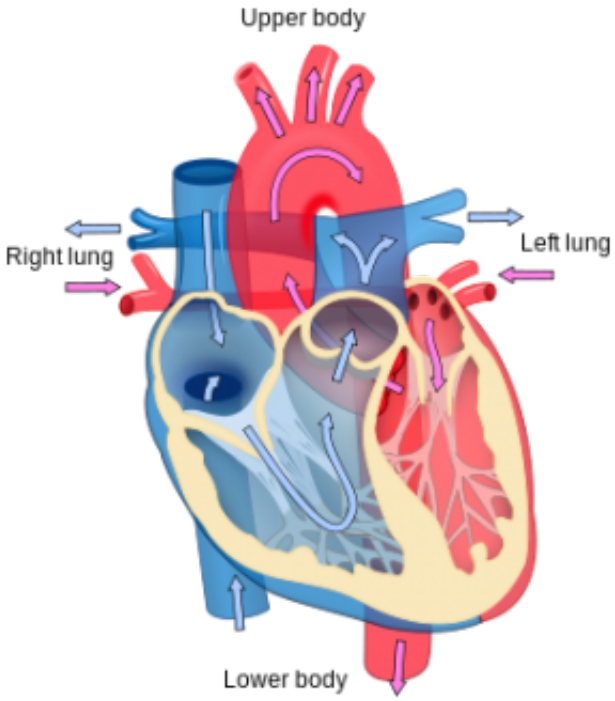

Heart diagram. Credit: Wikipedia

A Jackson Laboratory research team has found that the misfolded proteins implicated in several cardiac diseases could be the result not of a mutated gene, but of mistranslations during the "editing" process of protein synthesis.

In 2006 the laboratory JAX Professor and Howard Hughes Medical Investigator Susan Ackerman, Ph.D., showed that the movement disorders in a mouse model with a mutation called sti (for "sticky," referring to the appearance of the animal's fur) were due to malformed proteins resulting from the incorporation of the wrong amino acids into proteins as they are being produced.

In new research published in the *Proceedings of the National Academy of Sciences*, performed in collaboration with Paul Schimmel, Ph.D., and colleagues of The Scripps Institute, Ackerman and colleagues demonstrate that the same mechanism leads to misfolded proteins and cell death in the heart.

"We now have the second description of mistranslation causing pathology, this time in the heart," Ackerman says. "We know that in certain heart diseases, such as desmin-related cardiomyopathy and systemic amyloidosis, cardiomyocytes can accumulate malformed proteins. This is analogous to the toxic sludge of misfolded proteins that, in neurodegenerative diseases like Huntington's, kills neurons."

To understand the effects of mistranslation, the researchers tinkered with the ability of alanyl-tRNA synthetase, an enzyme involved in protein synthesis, to fix its mistakes. Alanyl-tRNA synthetase is supposed to load the amino acid alanine onto specific transfer RNAs (tRNAs), which then transport the alanine to ribosomes, where it is added to proteins under construction.

However, on occasion this enzyme puts the wrong amino acid on these tRNAs. When this occurs, the enzyme recognizes the error and removes the amino acid preventing it from being included at the wrong site in the protein. A severe reduction in this process, called editing, led to early embryonic lethality, suggesting that editing is important in multiple cell types, not just neurons.

"Then we asked, what if we take sticky mutation, which still has some editing potential, and lower the amount of the enzyme by half?" Ackerman says. "And we found that, indeed, this loss of editing activity did have an effect on the heart, leading to the death of cardiomyocytes and affecting the function of the heart."

The results suggest that genetic factors that disrupt the accuracy of translation may contribute to defects of the heart and possibly other tissues, as

well as the brain, Ackerman notes.

More information: Deficiencies in tRNA synthetase editing activity cause cardioproteinopathy, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1420196111

Provided by Jackson Laboratory