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Study finds harmful protein on acid triggers a life-threatening disease

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Using an array of modern biochemical and structural biology techniques, researchers from Boston University School of Medicine (BUSM) have begun to unravel the mystery of how acidity influences a small protein called serum amyloid A (SAA).

The findings, published in the journal *Proceedings of the National Academy of Sciences*, may help design new treatments for the life-threatening human disorder called secondary systemic amyloidosis (AA).

Amyloidoses are disorders in which abnormal proteins build up in tissues and organs. One of such disorders is AA amyloidosis, which is a complication of chronic inflammation that is common worldwide in developing countries.

This complication often occurs in patients already suffering from rheumatoid arthritis, Crohn's disease, inflammatory bowel disease, lupus, tuberculosis and other inflammatory diseases.

According to the researchers, acidic conditions favor misfolding and harmful accumulation of various proteins in AA, Alzheimer's disease, and many other deadly human disorders called protein misfolding diseases or amyloidoses. "The molecular underpinnings for this harmful process have up to now been unclear, limiting our ability to block or slow down the disease. However, we have now determined at a molecular level why acidic conditions favor formation of toxic misfolded aggregates of a protein called SAA. In short, we explained

why this small protein on acid can wreak havoc in the cell," explained Olga Gursky, PhD, professor of Physiology & Biophysics at BUSM and a principal investigator on this study.

The researchers found that at certain acidic conditions SAA forms very unusual small clusters which not only provide a storage form for the protein but also dissolve cellular membranes if the acidity is right. The right acidic conditions occur in parts of cells called lysosomes that normally degrade unwanted proteins. "Our results suggest how this cell defense fails in AA amyloidosis. At acidic pH, toxic protein clusters discovered in our study damage lysosomes and release their contents into cells, thus killing the cells and ultimately forming harmful plaques that spread to vital organs. These clusters may provide a missing link in our understanding of the initiation and progression of the major human disease called secondary amyloidosis, or AA," explained Shobini Jayaraman, PhD, senior scientist in Physiology & Biophysics who is the corresponding and lead author of this study.The researchers hope this study will help establish new therapeutic targets and, ultimately, find much-needed new treatments for this form of systemic amyloidosis. "The earlier we can block this harmful process, the better are our chances of actually helping patients."

More information: Shobini Jayaraman et al. Serum amyloid A forms stable oligomers that disrupt vesicles at lysosomal pH and contribute to the pathogenesis of reactive amyloidosis, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1707120114

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