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Molecular mechanism at root of familial amyloidosis and other diseases

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A team of local researchers has proposed a molecular mechanism that may be responsible for the development of life-threatening diseases called amyloidoses. The best known of such diseases is Alzheimer's disease (AD), but there are many others that are receiving increased scrutiny, in part because of mounting evidence linking them to atherosclerosis and aging.

The findings, which appear in the *Journal of Molecular Biology*, may ultimately lead to the development of therapeutic targets for one of these diseases.

A group of disorders, called amyloid diseases, occurs due to proteins that form abnormal clumps and deposit in different organs, causing damage to the brain (AD, Parkinson's disease), heart (cardiac amyloidosis), kidney, liver and other vital organs. One such protein called apolipoprotein A-1 (apoA-1) forms the scaffold of the so-called "good cholesterol," or high-density lipoprotein (HDL). Normally, apoA-1/HDL removes excess cholesterol and other fats from the body and is protective against cardiovascular disease. However, when mutations or other errors occur within this protein, apoA-1 has the potential to aggregate and manifest as familial form of amyloidosis, which is a life-threatening incurable disease. ApoA-I can also deposit in arteries, thereby contributing to atherosclerosis. While the medical community has known for some time that abnormal proteins can cause disease due to exposed vulnerable "hot spots" that clump together, there has been a lack of understanding about how a "good" protein can become so "bad,"

especially at a molecular level.

Using cutting-edge technology to study the dynamic behavior and molecular shape of apoA-1 and its various mutant forms, researchers at Boston University School of Medicine (BUSM) and Northeastern University were surprised to discover that exposed "hot spots" in apoA-I do not always cause amyloid disease. Some mutations led to decreased protection in other vulnerable parts, which helped the body to get rid of the protein before it clumps. These mutations in apoA-I did not cause amyloid disease in humans. The researchers suggest that this finding is not limited to apoA-I but possibly applies to other amyloid-forming proteins. Surprisingly, some mutations occurring at one end of the protein acted like "molecular remote-controls" and changed the structure and activity of the other end.

According to the researchers, solving the puzzle of the molecular changes that cause amyloid diseases has important implications for potential treatments. "If one could predict what makes any given protein to form amyloid, one could begin to design tools to decelerate or even block this pathogenic process before it starts," explained corresponding author Olga Gursky, PhD, professor of Physiology and Biophysics at BUSM.

More information: Structural Stability and Local Dynamics in Disease-Causing Mutants of Human Apolipoprotein A-I: What Makes the Protein Amyloidogenic? DOI: 10.1016/j.jmb.2015.10.029

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