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Culprit implicated in neurodegenerative diseases also critical for normal cells

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The propensity of proteins to stick together in large clumps—termed "protein aggregation"—is the culprit behind a variety of conditions including Huntington's, Alzheimer's, and mad cow diseases. With this notoriety, protein aggregation is considered to be a bad accident of nature that happens when protein structure is mismanaged. But new research published online on June 13th in the Cell Press journal *Developmental Cell* shows that, when kept in balance, protein aggregation has beneficial functions that allow cells to organize themselves in both time and space. The findings will be valuable as researchers design treatments for diseases that involve this process.

"We discovered that protein aggregation is a way cells can create spatial patterns in molecules called transcripts, which are the intermediaries between the DNA and proteins," says senior author Dr. Amy Gladfelter of Dartmouth College. Positioning transcripts in specific places allows the cells to control where the encoded proteins are made and can influence the localization and function of proteins. "This work redeems or elevates protein aggregation as not simply a terminal or negative function, but opens it up for examination as a mechanism exploited by cells for diverse purposes," says Dr. Gladfelter.

Key to this process is a repetitive stretch of a protein building block called glutamine, which is known to serve as a glue for protein aggregates in disease. Through studies in yeast, Dr. Gladfelter and her team found that this repetitive stretch of glutamine is also used to cluster proteins for a normal cellular process, namely the regulation of a cell's

division cycle. They note that many other proteins that are not associated with disease have similar glutamine stretches in their sequences.

"We hypothesize that many cell functions may be spatially organized by taking advantage of these repetitive glutamine tracts that are surprisingly common in many types of proteins," says Dr. Gladfelter.

As more examples of useful protein aggregation are identified, it should become clear how aggregates are regulated so that they do not reach toxic levels associated with diseases. "Understanding how this 'sweet spot' of aggregation is achieved will be useful for understanding pathways that are misregulated in established protein-aggregation disorders," explains Dr. Gladfelter. Also, as therapies are developed to treat protein-aggregation-based pathologies, it will be critical to consider that there may be many useful aggregates that should not be destroyed in the process of treating disease-causing aggregates.

More information: *Developmental Cell*, Lee et al.: "Protein aggregation behavior regulates cyclin transcript localization and cell-cycle control." dx.doi.org/10.1016/j.devcel.2013.05.007

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