Structure-based design and discovery of improved anti-amyloidogenic compounds

https://neurodegenerationresearch.eu/survey/structure-based-design-and-discovery-of-improved-anti-amyloidogenic-compounds/

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Canada

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Research Abstract

Proteins are the “machines” of the cell. Each protein has a distinct 3-dimensional shape, defined by its amino acid sequence. This amino acid sequence tells proteins how to fold into their correct shape so they can function. Sometimes proteins don’t follow their amino acid instructions and they accidently misfold into the wrong shape. These misfolded proteins tend to clump together with other misfolded proteins, much like the way milk curdles when heated. These protein clumps are called plaques and if plaques appear in the brain, they can cause serious problems. Alzheimer’s (AD), Parkinson’s (PD) and Creutzfeldt-Jakob disease (CJD) are all examples of progressive neurodegenerative diseases characterized by protein misfolding

and protein plaque formation. Each condition involves the misfolding of one or more disease-specific proteins. In Alzheimer’s disease it is the amyloid-beta protein, in Parkinson’s disease it is alpha-synuclein and in Creutzfeldt-Jakob disease it is the prion protein. Currently, no effective treatment is available to stop these diseases or prevent protein plaque formation. Recently several chemicals have been discovered that appear to prevent the misfolding of these disease-causing proteins. Some of them are naturally occurring compounds such as tetracycline (an antibiotic), EGCG (found in green tea) and curcumin (found in turmeric). Others are synthetic compounds such as ibuprofen and rifampicin. The question is: What is unique about these compounds that allows them to stop protein misfolding? Using structural biology techniques that allow us to see the atomic structures of proteins, we have started to determine where and how these chemicals bind to the properly folded and misfolded forms of these disease-causing proteins. If we can better understand their mechanism of action it may open the door to discovering even better anti-clumping compounds and eventually to the development improved therapies for AD, PD and CJD.

Further information available at:

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