Analytical Seminar

Thursday, Sept. 22, 2016

12:30 p.m. in Room 1315 Chemistry

"Homotypic and heterotypic interactions in amyloid protein networks"

Amyloid protein deposits are strongly associated with the pathology observed in Alzheimer's disease, senile systemic amyloidosis, Parkinson's disease, and other degenerative disorders. Although the proteins in each disease differ in sequence and native fold, and all have different normal biological functions, all can be triggered to misfold and self-associate into insoluble aggregates of cross-beta structure and fibrillar morphology. Along the path to fibrils, a diverse array of soluble oligomeric aggregates also arise. These aggregates are heterogeneous in size, structure, and morphology; moreover, most researchers now believe that it is these oligomeric intermediates that are most toxic.

Because of the close linkage between amyloid protein aggregation and neurodegenerative disease, there is intense interest in characterizing the mechanism of growth, the nature of the intermediates, and the kinetics of fibrillogenesis. This is a huge experimental challenge. I will describe some of our efforts to use light scattering and other techniques to capture key features of amyloid protein aggregation in solution.

Because amyloid proteins, upon misfolding, adopt similar conformations, we wondered whether they could interact heterotypically as well as homotypically. The biological relevance of heterotypic interactions is hinted at by studies which show that transgenic mice, engineered to express large quantities of the Alzheimer-related protein beta-amyloid, spontaneously upregulate expression of transthyretin, a transport protein that is the primary component of amyloid deposits in senile systemic amyloidosis. Moreover, transthyretin upregulation protects transgenic mice against neuronal damage that is otherwise caused by beta-amyloid. This observation suggests that, while homotypic interactions are pathological, heterotypic interactions between amyloidogenic proteins may actually be protective. I will discuss our efforts to define the molecular basis for heterotypic interactions between beta-amyloid and transthyretin, and to develop novel therapeutic compounds based on this understanding.

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