Chemistry / Biochemistry
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Chemistry of Neuro-Disorders: Their Mechanism, Diagnostics and Drug Development

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From Prions to Parkinson´s disease: Targeting protein aggregation in search for new therapeutics.

All common neurodegenerative diseases are characterized by the formation and deposition of fibrillar aggregates of specific proteins in the brain. For example, pathological aggregates of the prion protein are found in prion diseases such as Creutzfeldt-Jakob disease and mad-cow disease, and aggregated alpha-synuclein protein is found in Parkinson´s disease. These protein aggregates seem to be key players in the pathogenesis of neuronal dysfunction and neuronal cell death. Therefore, blocking the formation of pathological protein aggregates should be a new and promising approach for the therapy of these devastating diseases. We used the technique of confocal single molecule fluorescence fluctuation analysis to study protein aggregation at the single particle level. The basic idea behind this method is to analyse the signal fluctuations caused by the diffusion of single fluorescently labelled particles through an open measurement volume defined by the focus of a laser beam. This method lends itself to miniaturisation and automation and has become an established method for high-throughput screening in the pharmaceutical industry. We developed model systems consisting of fluorescently labeled proteins in suitable buffer conditions, and we could induce formation of pathological protein aggregates with toxic properties *in vitro*. We could then test a large number of diverse chemical compounds for potential inhibitory effects on aggregate formation. This resulted in the identification of new compounds which efficiently blocked aggregate formation and also exhibited beneficial therapeutic effects in cell culture and experimental animals.

References:

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