FASSBERG Seminar Series

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Phthalocyanines as Molecular Probes to Block Disease-Associated Protein Aggregation

The aggregation of proteins into toxic conformations plays a critical role in the development of different neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Creutzfled–Jakob's disease (CJD). These disorders share a common pathological mechanism that involves the formation of aggregated protein species including toxic oligomers and amyloid fibrils. The aggregation of alpha-synuclein (αS) in PD and the amyloid beta peptide (Aβ) and tau protein in AD results in neuronal death and disease onset. In the case of CJD, the misfolding of the physiological prion protein (PrP) induces a chain reaction that results in accumulation of particles that elicit brain damage. Currently, there is no preventive therapy for these diseases and the available therapeutic approaches are based on the treatment of the symptoms rather than the underlying causes of the disease. Accordingly, the aggregation pathway of these proteins represents a useful target for therapeutic intervention. Therefore, understanding the mechanism of amyloid formation and its inhibition is of high clinical importance. The design of small molecules that efficiently inhibit the aggregation process and/or neutralize its associated toxicity constitutes a promising tool for the development of therapeutic strategies against these disorders. In that direction, tetrapyrrolic compounds were forund to modulate the amyloid assembly of αS, tau, Aβ, and the PrP in vitro, and protect cells from the toxic effects of amyloid aggregates. In addition, in scrapie-infected mice, these compounds showed important prophylactic antiscrapie properties. The structural basis for the inhibitory effect of phthalocyanines on amyloid filament assembly relies on specific π–π interactions between the aromatic ring system of these molecules and aromatic residues in the amyloidogenic proteins. The tendency of phthalocyanines to oligomerize (self-association) via aromatic–aromatic stacking interactions correlates precisely with their binding capabilities to target proteins and, more importantly, determines their efficiency as anti-amyloid agents. The ability to block different types of disease-associated protein aggregation raises the possibility that these cyclic tetrapyrrole compounds have a common mechanism of action to impair the formation of a variety of pathological aggregates.

Host: Christian Griesinger

Large Seminar Room, Administration Building
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