Identification of $\alpha$-synuclein filament-binding proteins: Possible pathological contributions to Parkinson's disease

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ABSTRACT

This dissertation is based on three papers.

$\alpha$-synuclein is a small presynaptic brain protein. Aggregates of $\alpha$-synuclein accumulate in cytoplasmic inclusions Lewy bodies, in Parkinson's disease and Lewy body dementia and mutations in its gene cause autosomal dominant early-onset Parkinson's disease and Lewy body dementia. This demonstrates a direct link between dysmetabolism of $\alpha$-synuclein and neurodegeneration and strongly implicates the process of aggregation of monomeric $\alpha$-synuclein species in the cellular demise.

Very little is known about the functions of aggregated $\alpha$-synuclein, in contrast to the monomeric species, although this may be important for our understanding of the pathogenesis of neurodegenerative disorders.

This PhD project focused on the identification of brain ligands for aggregated $\alpha$-synuclein and subsequent analysis of the interactions and their functional effects using a broad range of biochemical techniques. Three molecules among these were selected for more detailed analysis, the brain specific protein p25$\alpha$, the high mobility group protein 1 (HMGB-1) and the 20S proteolytic core particle of the 26S proteasome. All three protein species bound directly to $\alpha$-synuclein aggregates and they displayed a preference for binding to $\alpha$-synuclein in its aggregated state compared to the monomeric form. Moreover, they all displayed an abnormal subcellular localization in the degenerating neurons in Parkinson's disease and Lewy body dementia, where they accumulated in the Lewy body inclusions along with aggregated $\alpha$-synuclein.

Cloning and expression of the human p25$\alpha$ enabled a detailed analysis that demonstrated that p25$\alpha$ potently stimulates aggregation of $\alpha$-synuclein. P25$\alpha$ may thus act upstream in the aggregative process where a dysregulation of p25$\alpha$ expression could act as a disease trigger or accelerator. By contrast, the other ligands HMGB-1 and the proteasome may be affected downstream of the aggregated $\alpha$-synuclein that disturbs their normal function. HMGB-1 is a cotranslational regulator of steroid receptor function and the proteasome plays a pivotal role in the catabolism of misfolded cellular proteins so aggregated $\alpha$-synuclein holds the potential of deranging fundamental cellular processes. Interestingly, among the $\alpha$-synuclein aggregate binding proteins were some that counteracted the inhibitory effect on the proteasome and thus may represent cellular defenses against aggregated $\alpha$-synuclein.

The data may contribute to the development of strategies aimed at both inhibiting the pathogenic aggregation of $\alpha$-synuclein and the toxic properties of these aggregates.