Deep mutational scanning reveals toxic conformation of alpha-synuclein

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Intrinsically disordered proteins can adopt different conformation in cells. Some of these conformations fulfill beneficial functions in cells, while others are misfolded and can be toxic and be linked to diseases, such as neurodegenerative disease. It is very challenging to characterize the structure of protein conformations with specific activities using traditional approaches, since active conformations may only represent a minority.

In a collaboration between the Kampmann and Degrado labs led by postdoc Robert Newberry, with contributions from Jaime Leong and Eric Chow, deep mutational scanning uncovered the conformation of the protein alpha-synuclein that is toxic in yeast cells: a long amphiphilic alpha-helix, likely mediating membrane binding. Misfolding of alpha-synuclein is linked to Parkinson’s Disease, and a yeast model of alpha-synuclein toxicity has provided useful insights.

This study was published in Nature Chemical Biology [1]:

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[1] https://www.nature.com/articles/s41589-020-0480-6