University of Massachusetts UMASS Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

NOAH COHEN

MENTOR: C. Robert Matthews, PhD
Wednesday, September 11, 2019 10:00 a.m.
LRB 816

Exploring the complex folding free energy landscapes of a series of β-rich proteins

Protein aggregation is deleterious to human health and detrimental to therapeutic shelf-life. The physical processes that induce aggregation are the same processes that drive productive folding reactions. As such, protein aggregation is a non-productive form of protein folding. To gain insight into the steps that serve as a partition between the folding and aggregation reactions, the folding mechanisms of several β-rich proteins with links to human disease or medicine were examined.

In the ALS-linked protein, SOD1, a subpopulation of the unfolded ensemble is found to be a common source of both nonnative structure and frustrated folding. These behaviors are only observed upon the reduction of the intrinsic disulfide bond, indicating that this covalent interaction wards against aggregation. The nonnative structure presents an attractive target for the development of new therapeutic agents.

In V_H domains from therapeutic mAbs, the intramolecular disulfide bond protects against aggregation. However, it can also introduce complexity to the folding mechanism. This complexity is linked to the formation of a strained orientation of the disulfide bond. This strained orientation of the disulfide in certain V_H domains is energetically unfavorable enough to disrupt the formation of the disulfide in the full length mAbs. The novel relationship observed between disulfide orientation, folding complexity, and incomplete oxidation warrants further examination in other Ig domains.

Overall, these results demonstrate that mapping the folding free energy landscape for proteins with roles in human disease or therapeutics can provide valuable insights for developing and improving treatment options.

Mentor(s)

C. Robert Matthews, PhD

Dissertation Exam Committee

Francesca Massi, PhD (Chair)
Celia Schiffer, PhD
David Lambright, PhD
Lawrence Hayward, MD, PhD
Susan Marqusee, MD, PhD