Clarifying solubility and aggregation in the crystallin proteins of the eye lens

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Description:
Research in the Martin lab is focused on understanding protein systems using NMR and other biophysical techniques. In particular, we are interested in concentrated, semisolid systems that are difficult to study using conventional structural methods. Examples include membrane proteins in their native environments and the transparent hydrogel formed by the crystallin proteins making up the vertebrate eye lens. In the context of human health, the loss of crystallin solubility leads to cataract, a major cause of blindness worldwide. Eye lens proteins exist in a densely packed environment with very little protein turnover; understanding the fundamentals of how they remain stable and soluble for a lifetime is essential to preventing cataract and other protein deposition diseases. We use point mutations associated with hereditary cataract to probe key molecular properties driving crystallin solubility and aggregation. In a complementary effort, we use molecular modeling and protein structure network analysis to discover novel proteases from genomic data, with the objective of finding proteases that are better able to degrade recalcitrant protein aggregates such as amyloid fibrils and cataract.

We also investigate how the lens proteins of non-human animals enable them to withstand extreme environments. For instance, the Antarctic toothfish swims in the Southern Ocean at -2 ºC, yet its eye lenses resist cold cataract, a reversible liquid-liquid phase separation (LLPS). In contrast, mammalian eye lenses experience this phenomenon at approximately 20 ºC. Although the whole lens is completely resistant to cold cataract down to its freezing point, in isolation some of the component proteins are more resistant than others. Furthermore, we were able to change the least cold-tolerant toothfish γM-crystallin into one that is more resistant to LLPS than any seen in the natural system by mutating only three surface residues. This result has potential significance beyond the study of eye lens proteins and cold-adapted organisms, because this type of protein-based LLPS is also observed in membraneless organelles, which serve as sub-cellular compartments for transiently concentrating particular molecular species in response to external stimuli. In the γM-crystallin system, we can now tune the onset temperature of LLPS, under conditions where the protein is well-folded, by ± almost 10 ºC, using a small number of mutations. In the future, this may lead to the creation of artificial membraneless organelles or miniature bioreactors.