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Gamma Crystallin Modifications & Mechanisms of Lens Opacity

The long-term objective of this proposal is to determine the molecular mechanisms by which modifications of the γ -crystallins (genetic or age-onset), lead to cataract formation. Proposed here are studies on modified γ -crystallins known to be associated with either genetic or age-onset cataract. In Aim 1 interactions between modified γ -crystallins alone will be examined (self-association), and in Aim 2 interactions of modified γ -crystallins with γ -crystallin will be examined. Most studies to date have been of the first type and have led to a better understanding of how modified γ -crystallins self-associate and form “condensed phases” which are responsible for light scattering and opacity. The second type of interaction has recently emerged as being equally important in maintaining lens transparency. Based on current knowledge, we propose the following hypothesis: *Modifications of the γ -crystallins alter the protein-protein interactions and lead to either (a) self-association of mutant proteins to yield a variety of condensed phases or (b) a change in the net attractive interactions between mutant γ -crystallins and γ -crystallin.* Experiments in Aim 1 will compare the thermodynamic phase diagrams, the low and high-resolution structures (using u.v.-visible, circular dichroism, fluorescence, FTIR, Raman and NMR), and stabilities of the modified forms of human γ D, γ C, and γ S crystallins, with those of the wild-type protein. Phase diagrams provide the boundary conditions for the formation of condensed phases which lead to light scattering and opacity. Therefore, these studies and light scattering measurements (static and dynamic) are an integral part of the proposed studies. In Aim 2, the interactions of those modified forms of γ -crystallins which do not self-associate will be examined with native γ -crystallin, also using similar techniques.

Thus, the proposed experiments will identify molecular mechanisms that lead to light scattering and opacity due to γ -crystallin modifications in the lens, and should provide a comprehensive understanding of both forms of cataract disease – genetic, as well as age-onset cataract.