"Folding, Unfolding and TriC Chaperonin Recognition of Human γD-Crystallin in Relation to Cataract"

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The eye lens crystallins are among the longest-lived proteins in the human body. The γ- and β- crystallins are essentially all β-sheet proteins with duplicated double Greek key domains. Certain single amino acid substitutions cause juvenile-onset cataracts in mice and in humans. The γ-crystallins all exhibit a set of four buried tryptophans whose excited states are linked through a charge transfer network, sharply quenching their fluorescence. This provides a very sensitive signal for crystallin conformation, permitting the characterization of partially folded intermediates during in vitro unfolding and refolding. Despite their native state stability, partially unfolded γ-crystallin molecules accumulate as high molecular weight aggregates in the elderly, generating cataracts, the leading cause of blindness in the world. In younger people this process is probably retarded by the presence of high concentrations of the small heat chaperone αA, B- crystallin. This passive soccer ball-like oligomeric complex binds partially unfolded proteins, suppressing aggregation, but cannot refold the proteins. Recently we have found that the human group II chaperonin TRiC (or CCT), required for the folding of tubulin, actin and other essential proteins, also suppresses the off-pathway aggregation of the γ-crystallins, and, in the presence of ATP, refolds them back to the native state. This reaction is likely to be physiologically protective for cortical cataract, but also provides an assay for the further characterization of this critically important eukaryotic chaperonin.