The Role of Native Lens α-crystallin in Amyloid Suppression Using β-amyloid as a Model Amyloid Client

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INTRODUCTION

Cataracts are a result of age-related protein aggregate formation in the eye lens, and the leading cause of blindness worldwide. α-crystallin acts as a molecular chaperone that serves as the primary defense mechanism against protein aggregate formation in the lens. Recent evidence suggests amyloid formation in the lens may contribute to cataract formation, and that β-amyloid is present in lens epithelial-aged cataracts. Previous studies have shown that αB-crystallin in other parts of the body, such as the brain, is protective against neurodegenerative diseases such as Alzheimer’s disease that are associated with plaque deposits containing β-amyloid. In vitro, αB-crystallin inhibits fibril elongation of β-amyloid. However, the capacity of native lens crystallins protects against β-amyloid formation is still unclear. The aim of this thesis was to determine if the native lens specific αL-crystallin, a 1:1 ratio of the isoforms αA and αL-crystallin, would prevent the fibril elongation of β-amyloid compared to αB-crystallin.

RESULTS

To quantify the efficiency of αL-crystallin as a molecular chaperone for β-amyloid compared to αB-crystallin, the half-times (T1/2) of fibril formation for each of the experimental conditions were determined using the AmyloFit program. The T1/2 values for both αL- and αB-crystallin showed a dose-dependent response leading to T1/2 values that were all longer than the β-amyloid control. The chaperone αB-crystallin showed a longer half-time than β-amyloid for the 20x and 50x conditions, and at 100x completely suppressed fibril formation. Thus, both chaperones were effective at reducing the kinetics of fibril nucleation/elongation. However, αL-crystallin was not as effective of a chaperone as αB-crystallin.

CONCLUSION

The chaperone activity of αL-crystallin was further evaluated by using Thioflavin T Fluorescence. At the molecular level, cataract formation is the result of age-related protein aggregation within the eye lens. The chaperone αL-crystallin interacted with β-amyloid as a molecular chaperone in a similar manner that was all longer than the β-amyloid control. The chaperone αB-crystallin showed a longer half-time than β-amyloid for the 20x and 50x conditions, and at 100x completely suppressed fibril formation. Thus, both chaperones were effective at reducing the kinetics of fibril nucleation/elongation. However, αL-crystallin was not as effective of a chaperone as αB-crystallin.

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