

P008 TTR proteolytic activity enhances apoA-I fibril formation
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Proteolysis has been thought to play an important role in most types of amyloidoses; in several cases, an amyloid peptide is generated by proteolytic cleavage of the corresponding protein precursor. One disorder included in this group is apolipoprotein A-I (apoA-I) - related amyloidosis. We have previously determined that transthyretin (TTR) is associated with apoA-I biology: i) a fraction of plasma TTR circulates in high density lipoproteins (HDL) through binding to apoA-I, ii) TTR is able to cleave the C-terminus of apoA-I after the residue Phe225, and iii) under pathological conditions, a new amyloidogenic apoA-I variant has been identified, where fibrils presented both mutant apoA-I N-terminal fragments and wild-type (WT) TTR. We therefore hypothesized that by cleaving apoA-I TTR might influence its deposition as amyloid. To evaluate this hypothesis, the amyloidogenicity of full length apoA-I and of TTR-cleaved apoA-I was compared by analysis of fibrillar growth by transmission electron microscopy. We observed that cleaved apoA-I forms fibrils faster than the full-length protein. Moreover, apoA-I immunohistochemical analysis of amyloid deposits in tissues from patients with different amyloidoses not related with apoA-I mutations, showed apoA-I co-deposition. Studies with monoclonal antibodies directed against either the N- or C-terminus of apoA-I are currently underway to evaluate the possibility that apoAI might be cleaved. This work demonstrates that proteolysis by TTR may impact on apoA-I amyloidosis and possibly in the co-deposition of apoA-I in other amyloidoses