The dark side of protein folding: studies with amyloidogenic proteins Débora Foguel

Instituto de Bioquímica Médica, Universidade Federal do Rio de Janeiro, Brasil

The formation of amyloid aggregates is the hallmark of the amyloidogenic diseases. Transthyretin (TTR) is involved in senile systemic amyloidosis (wt) and familial amyloidotic polyneuropathy (variants). Through the use of high hydrostatic pressure (HHP), we compare the stability among wt TTR, two disease-associated mutations (V30M and L55P) and a trans-suppressor mutation (T119M). Our data show that the amyloidogenic conformation, easily populated in the diseaseassociated variant L55P, can be induced after decompression, rendering the wt protein highly amyloidogenic. After decompression, the recovered wt structure has weaker subunit interactions (it forms a looser tetramer called T4*) and its stability is similar to L55P. The observed sequence of stability was: L55P < V30M < wt << T119M. After a cycle of compression-decompression at 37 cC and pH 5.6, TTR (wt and variants) undergoes aggregation very rapidly (~ 30 min). This HHP protocol has allowed us to screen several anti-amyloidogenic compounds, including the well-known NSAID. Although all amyloid fibrils exhibit a common architecture (cross beta-sheet topology), we decided to investigate whether they display differences in stability that might be correlated with their primary sequences. Indeed, this was the case for the fibrils composed by TTR or by alpha-synuclein, involved in Parkinson disease. We have also shown that the fibrils and the protofibrils have different stabilities. The relevance of these differences in stability to pathogenesis will be discussed.

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