PRODUCTION OF HETEROTETRAMERS AS A STRATEGY TO PREVENT FAMILIAL AMYLOIDOTIC POLYNEUROPATHY, A FATAL AMYLOIDOGENIC DISEASE

Palhano,F.L, Leme,L.P., Busnardo,R.G. Azevedo,E.P.C. and Foguel,D.*
Instituto de Bioquímica Médica, UFRJ, RJ, Brazil;
*foguel@bioqmed.ufrj.br

Transthyretin (TTR) is a 127-residue homotetrameric β-sheet-rich protein that transports thyroxine in the blood and cerebral spinal fluid. Familial amyloidotic polyneuropathy is a hereditary form of amyloidosis associated with one over 80 different point mutations in TTR, being V30M the most frequent and L55P the most aggressive in the symptoms evoked. Conversely, the variant T119M is very stable and non-amyloidogenic. Thus, this mutation seems to be suitable to prevent tetramer aggregation. At pH5.0, the combination of high hydrostatic pressure, 4M urea and 1°C, the tetramers of T119M were irreversible dissociated into unfolded monomers. Upon urea dilution at pH7.0, these monomers initially refold back into folded monomers and then slowly (hours) reassemble into native tetramers. Since at pH7.0 the monomers of T119M last for a period of time, we thought to produce heterotetramers by mixing the monomers of T119M with L55P and V30M. Heterotetramers composed of T119M and L55P subunits were observed and these tetramers displayed a decreased yield of fibril formation, suggesting that the presence of T119M subunits within the tetramer is an interesting strategy to prevent aggregation of TTR. Interestingly, when incubated at pH4.0, the "non-amyloidogenic" T119M monomer undergoes aggregation forming amyloid fibrils as observed with other variants of TTR. These data will be presented in combination with all the dissociation-unfolding profile of T119M tetramers and monomers.
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