Protein Misfolding Diseases: The Case of Transthyretin

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Transthyretin (TTR) is a tetrameric protein composed of identical 127-residue subunits having predominantly a beta-sheet structure. Wild-type TTR is responsible for senile systemic amyloidosis (SSA), a disease that affects 25% of people over 80 years old, and is characterized by heavy amyloid deposits in the heart. On the other hand, more than 100 point mutants of TTR have been described thus far, most of them involved in familial amyloidotic polyneuropathy (FAP). On the other hand, the non-amyloidogenic mutant T119M has been described as an interallelic trans-suppressor variant in compound heterozygotes displaying high frequency of occurrence in Portuguese population and ameliorates the effects of the pathogenic mutation, reducing severity of the symptoms. High Hydrostatic Pressure (HHP) has been used successfully to denature and dissociate proteins, protein-DNA complexes, virus particles and, more recently, protein aggregates and amyloid fibrils. In the last years, our group has used HHP to probe the folding, dimerization, tetramerization and fibrillation of TTR (wt and variants). Our main findings were: 1. TTR dissociates under pressure and the difference in stability among the variants correlates with amyloidogenicity; 2. after a cycle of compression-decompression, TTR forms an altered tetramer which is aggregation prone; 3. since after pressure release TTR aggregates in less then 30 min, this protocol has been used successfully for drug screening; 4. the amyloid fibrils composed of wt or variant proteins respond differently to HHP treatment; 5. T119M is pressure-resistant, but by adding sub-denaturing concentrations of urea, it dissociates into monomers, which were successfully incorporated into the amyloidogenic variants rendering them less amyloidogenic; 6. the variant A25T associated with leptomeningeal amyloidosis activates microglia cells, 7. TTR binds metal ions at specific sites which alters its stability and amyloidogenicity. Part of these data will be presented and discussed. Supported by: CNPq; CAPES, FAPERJ