Influence of Histidine Tautomerism on Protein Misfolding

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Abstract

Recently, we suggested histidine tautomerism as another possible factor influencing misfolding and oligomerization during the pathogenesis of amyloidogenic diseases. Our lab demonstrated that these different protonated states in the histidine imidazole ring can be related to the conformational characteristics of diverse misfolded peptides (namely Amyloid beta (Aβ), tau, amylin, prion, etc.) and may influence fibrillization processes in polypeptides, resulting in proteopathies. We also performed MD simulations on His tautomeric isomers εε, εδ, δε, and δδ of profilin-1 (PFN1) to explain the structural changes and to correlate them with its aggregation propensity. MD simulations show that His133 presumably plays a major role in the aggregation of PFN1 upon His tautomerism compared to His119 and propose that PFN1 His tautomers can provide a detailed microscopic understanding of the aggregation mechanisms which is difficult to be probed through experiments. We also compared β-sheet formation and histidine site-specific two-dimensional infrared (2D IR) spectroscopic signatures of Aβ dimers with different histidine states (δ; $N^{\delta 1}$-H, ε; $N^{\varepsilon 2}$-H, or π; both protonated). Characteristic blue-shifts in the 2D IR central bands were observed upon monomer-dimer transformation. The εεε:εεε dimer exhibited larger frequency shifts than δδδ:δδδ and πππ:πππ implying that the red-shift may have a correlation with $N^{\delta 1}$-H (δ) protonation. Finally, for the first time, the effect of the static external electric field (EF) of varying intensities and directions on the conformational integrity and dynamics of two tautomeric isomers (εεε, δδδ) of β-Amyloid40 (Aβ) will be discussed.