Nucleic Acid Binding and Hydration in Protein Misfolding: Insights from Studies of Prion and p53 Tumor Suppressor Proteins

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Protein misfolding has been implicated in a large number of diseases, which are now grouped under the name of protein folding disorders (PFDs). In these diseases, large quantities of wrongly folded proteins undergo aggregation, destroying brain cells and other tissues. Such disorders include Alzheimer's disease, Parkinson's disease, transmissible spongiform encephalopathies, familial amyloid polyneuropathy, Huntington's disease, and type II diabetes, and cancer. To approach the changes in hydration, packing and volume both when proteins fold correctly or when folding goes wrong leading to the protein folding disorders, we have used several biophysical and structural tools, including hydrostatic pressure. More recently, the main focus of our group is on the interplay between ligand binding and hydration in the formation of protein misfolding species. Whereas in many cases, ligand binding, such as a nucleic acid, acts by preventing wrong folds and aggregation, there are several cases in which they induce misfolding and assembly into amyloids. This simply occurs because the formation of structured aggregates, such as protofibrilar and fibrilar amyloids, involves decreases in hydration, formation of an H-bond network in the secondary structure, and burying of non-polar amino acid residues, processes that also occur in the normal folding landscape. We will present recent work on the folding and misfolding of two proteins, mammalian prion protein and tumoral suppressor protein p53, and how nucleic-acid binding and hydration influence the fate of the protein. We also discuss the implication of these findings for our understanding of the normal and wrong folding of these proteins in normal physiological states and in human disease, such as prion disorders and cancer. Acknowledgments: Supported by CNPq, FAPERJ and FINEP.