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| Title: | Molecular Origin of Internal Friction in Intrinsically Disordered Proteins |
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| Abstract: | The work presented in this dissertation involves the study of dynamical aspects of an intrinsically disordered protein namely human α-synuclein, which is a highly conserved pre- synaptic protein, and its aggregation is observed in the devastating Parkinson's Disease (PD) and other synucleinopathies. 1 Conformational dynamics of polypeptide chains is a diffusion- controlled process in the dense aqueous environment. Kramers' theory (Figure 1) provides a theoretical framework to explain such diffusion-controlled processes and states that the rate of protein folding or conformational relaxation is inversely proportional to solvent viscosity and directly proportional to "attempt frequency" of free energy barrier crossing 2,7 . Dynamical fluctuations giving rise to conformational changes in proteins are affected due to thermal changes and viscous drags experienced by proteins. 3 As opposed to simple polymeric systems or small molecules wherein the dynamics largely depends upon the solvent viscosity, proteins might show presence of certain internal energy dissipation mechanisms which will ultimately affect the conformational relaxation of polypeptides chains. This internal energy dissipation mechanism which offers inherent resistance to polypeptide chain towards changing its configuration is termed as internal friction. 4 Internal friction has been known to have an effect on the rate of conformational changes in proteins. 5 however, the molecular origin of this phenomenon remains elusive. The presence of internal friction can be attributed to several factors such as interchain collisions, dihedral angle rotations 27 , hydrogen bonding etc. 6, 25 The aim of this study was to understand whether dihedral rotations of the polypeptide backbone contribute to the internal friction in case of a model IDP, namely α-synuclein. In order to unravel the dihedral rotational dynamics, we took advantage of the powerful time- resolved fluorescence anisotropy measurements. The relationship between rotational dynamics and solvent viscosity is given by the Stokes-Einstein-Debye model. vThe model relates the rotational correlation time of a particle to the bulk viscosity of the surrounding medium. 8 One of the most common and model independent ways to characterize internal friction is by plotting the rotational correlation time (φ) as a function of solvent viscosity. 10 Internal friction component is then obtained as an intercept on the Y-axis. In our experimental results we observed that the slow rotational correlation time component (φ slow ) of fluorophore-tagged protein does scale linearly with the solvent viscosity but an intercept is obtained on the Y-axis if the plot is extrapolated to zero viscosity. The slow rotational correlation time component (φ slow ) is known to correspond to the dihedral rotational relaxation time scale of the protein backbone in case of expanded IDPs. 11 Therefore even at zero viscosity, the protein seems to offer resistance towards changing its conformation. We suspect that this internal resistance offered by the protein arises due to the Φ-Ψ dihedral rotations of the polypeptide backbone over the Ramachandran dihedral space ultimately contributing to internal friction. (b) (a) (c) Figure 1: (a) Diffusional barrier crossing problem for a one dimensional reaction coordinate 10 in the context of protein folding. (b)Mathematical representation of Kramers'reaction rate theory where k is the rate of barrier crossing and constant A depends upon the curvatures of free energy function (ω a and ω b ). (c) Linear fit between rotational correlation time and solvent viscosity yields internal friction as an intercept on the Y-axis. |
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