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All-atom Simulations unveil Physiological and Pharmacological Role of Protein Folding Intermediates

Over the last decade, the combined development of accurate time- resolved experimental techniques and advanced algorithms for computer simulations has opened the possibility of investigating biological mechanisms at atomic resolution with physics-based models. In particular, combination of experimental information and enhanced sampling techniques now allow the reconstruction of the co- translational folding pathways of biologically relevant proteins, at an atomic level of resolution. These innovative computational technologies reveals the existence of non-native metastable states transiently appearing along the co-transcriptional folding process of such proteins. The lifetime of these intermediates is set by the amino- acid synthesis rate, hence is in the several second time scale. In this talk, we review the evidence indicating that these protein folding intermediates play roles in post-translational regulation. We also discuss how the information encoded into protein folding pathways is being exploited in an entirely new generation of drugs capable of promoting the selective degradation of protein targets.

[1] G. Spagnolli et al., "Pharmacological inactivation of the prion protein by targeting a folding intermediate", Communications Biology 4 (1), 6223–124 (2021). DOI:10.1038/s42003-020-01585-x. [2] E. Biasini and P. Faccioli "Functional, pathogenic, and pharmacological role of protein folding pathways". Proteins. 2023; 1-9.

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