Structure-function relationship of biomacromolecules: dynamics play a crucial role too

Bidyut Sarkar
Molecular Spectroscopy Laboratory, RIKEN, Wako, Japan

Biomacromolecules, such as DNA, RNA, and proteins, perform complex cellular functions by adopting specific structures and/or by undergoing structural changes on relevant time scales. In this presentation, I will discuss my efforts toward understanding this structure-dynamics-function relationship of biomolecules using fluorescence spectroscopy and microscopy.

In the first part of the talk, I will present my PhD work on biophysical mechanisms of protein aggregation diseases, using amyloid-β, implicated in Alzheimer's disease, as a model peptide. I will discuss three major questions: (I) which earliest aggregate of amyloid-β is toxic?[1] (II) why is it toxic?[2,3] and, (III) how is it toxic?[4,5] Our results suggest that a key structural change at the earliest step of aggregation possibly drives amyloid-β toward the toxic pathway.

In the second part, I will introduce a state-of-the-art single-molecule fluorescence method called two-dimensional fluorescence lifetime correlation spectroscopy (2D FLCS).[6] This method, developed at my postdoctoral laboratory, can reveal biomolecular structural dynamics with an unprecedented microsecond time resolution. I will talk about my contributions in further advancing this cutting-edge method, and applying it to address important biological questions. I will discuss the development of dynamic-qenching 2D FLCS, which can report microsecond-resolved local structural change of biomolecules with single dye labeling.[7] I will also discuss the application of 2D FLCS in elucidating the folding energy landscape of the ligand-binding "aptamer" domain of prequeosine riboswitch, which is a therapeutically important noncoding RNA. We propose that a microsecond structural change of the aptamer domain likely governs the biological function of the riboswitch, i.e., to regulate transcription in bacteria.[8]

References

[1] B. Sarkar, A. K. Das, and S. Maiti, *Front. Physiol.* 4 (84), 1-11 (2013).
[2] S. Nag[#] and B. Sarkar[#] *et al*, *Phys. Chem. Chem. Phys.* 15, 19129-19133 (2013). ([#]equal contribution)
[3] B. Sarkar[#], B. Chandra[#], and V.S. Mithu[#] *et al*, *Angew. Chem.* 53, 6888-6892 (2014). ([#]equal contribution)
[4] B. Sarkar *et al*, *Front. Physiol.* 3 (414), 1-13 (2012).
[5] B. Sarkar[#] and A. Banerjee[#] *et al. ACS Chem. Neurosci.* 5(5), 329-334 (2014). ([#]equal contribution)
[6] K. Ishii and T. Tahara, *J. Phys. Chem. B* 117, 11414-11422 & 11423-11432 (2013).
[7] B. Sarkar, K. Ishii, and T. Tahara, *J. Phys. Chem. Lett.* 10, 5536-5541 (2019).
[8] B. Sarkar, K. Ishii, and T. Tahara, *J. Am. Chem. Soc.* 143, 7968-7978 (2021).