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| Title: | Excitation Energy Migration Unveils Fuzzy Interfaces within the Amyloid Architecture |
| Authors: | Das, Debapriya (/jspui/browse?type=author&value=Das%2C+Debapriya)<br>Madhu, Priyanka (/jspui/browse?type=author&value=Madhu%2C+Priyanka)<br>Avni, A. (/jspui/browse?type=author&value=Avni%2C+A.)<br>Mukhopadhyay, S. (/jspui/browse?type=author&value=Mukhopadhyay%2C+S.) |
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| Abstract: | Amyloid fibrils are highly ordered nanoscopic protein aggregates comprising a cross-β amyloid core and are associated with deadly human diseases. Structural studies have revealed the supramolecular architecture of a variety of disease-associated amyloids. However, the critical role of transient intermolecular interactions between the disordered polypeptide segments of protofilaments in directing the supramolecular structure and nanoscale morphology remains elusive. Here, we present a unique case to demonstrate that interchain excitation energy migration via intermolecular homo-Förster resonance energy transfer can decipher the architecture of amyloid fibrils of human α-synuclein. Site-specific homo-Förster resonance energy transfer efficiencies measured by fluorescence depolarization allowed us to construct a two-dimensional proximity correlation map that defines the supramolecular packing of α-synuclein within the fibrils. These studies captured unique heterotermainal cross talks between the fuzzy interprotofilament interfaces of the parallel-in-register amyloid spines. Our results will find applications in discerning the broader role of protein disorder and fuzziness in steering the distinct polymorphic amyloids that exhibit strain-specific disease phenotypes. |
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