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The Role of Tdp-43 Low-complexity Domain Nano-clusters In Its Phase Behavior

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Biomolecular condensation can organize macromolecules into a dense, droplet-like phase (condensates) and a dilute phase. There is limited information on intermediates formed in the transition from monomers to droplets. Here, we report that TDP-43-LC domain exists as heterogeneous clusters sized between 50 and 200 nm, as shown by the DLS, super-resolution microscopy, and electron microscopy. Tuning the solution pH drives these flexible nanoclusters to undergo different phase transitions, such as gelation or condensation. Condensate-promoting (G335A) and condensate-disrupting (A326P & W334G) mutants also formed dynamic nanoclusters with varied sizes and topologies. These mutants produced amyloid aggregates at pH 6 without forming droplets. We propose that the properties of these nanoclusters, including their size, charge, and monomer conformation, tune their phase behavior. High pH or salt neutralizes their charge, causing them to quickly collapse into droplets and subsequently to amorphous aggregates. In contrast, a highly charged environment (lower pH) increases their solubility, promoting slow interactions that facilitate their ordered assembly. We suggest that these nanoclusters are kinetically trapped entities whose assemblies can explain various phase transitions, such as gelation, aggregation and origin of different condensate features, including hollow condensates.