Title:	Synergistic Amyloid Switch Triggered by Early Heterotypic Oligomerization of Intrinsically Disordered α-Synuclein and Tau
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Keywords:	Parkinson's disease Amyloid formation Fluorescence spectroscopy Intrinsically disordered Proteins Oligomers
Issue Date:	2018
Publisher:	Academic Press
Citation:	Journal of Molecular Biology, 430(16), pp. 2508-2520
Abstract:	Amyloidogenic intrinsically disordered proteins, α-synuclein and tau are linked to Parkinson's disease and Alzheimer's disease, respectively. A body of evidence suggests that α-synuclein and tau, both present in the presynaptic nerve terminals, co-aggregate in many neurological ailments. The molecular mechanism of α-synuclein-tau hetero-assembly is poorly understood. Here we show that amyloid formation is synergistically facilitated by heterotypic association mediated by binding-induced misfolding of both α-synuclein and tau K18. We demonstrate that the intermolecular association is largely driven by the electrostatic interaction between the negatively charged C-terminal segment of α-synuclein and the positively charged tau K18 fragment. This heterotypic association results in rapid formation of oligomers that readily mature into hetero-fibrils with a much shorter lag phase compared to the individual proteins. These findings suggested that the critical intermolecular interaction between α-synuclein and tau can promote facile amyloid formation that can potentially lead to efficient sequestration of otherwise long-lived lethal oligomeric intermediates into innocuous fibrils. We next show that a well-known familial Parkinson's disease mutant (A30P) that is known to aggregate slowly via accumulation of highly toxic oligomeric species during the long lag phase converts into amyloid fibrils significantly faster in the presence of tau K18. The early intermolecular interaction profoundly accelerates the fibrillation rate of A30P α-synuclein and impels the disease mutant to behave similar to wild-type α-synuclein in the presence of tau. Our findings suggest a mechanistic underpinning of bypassing toxicity and suggest a general strategy by which detrimental amyloidogenic precursors are efficiently sequestered into more benign amyloid fibrils.
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