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Surface Adsorption Is a Key Determinant of A-synuclein Condensate Maturation into Toxic Aggregates

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α-Synuclein (αS) self-assembles into amyloid fibrils during neurodegeneration. αS can also self-assemble via liquid-liquid phase separation (LLPS) to form condensates. The link between these processes is evident, as αS condensates can mature into amyloids. Yet, the mechanisms driving this maturation are largely unknown, particularly when including post-translational modifications known to affect αS self-assembly in the absence of LLPS, e.g., N-terminal truncation (NTT). Moreover, condensates are primarily studied as isolated entities; however, it is increasingly clear that they interact with various cellular components and surfaces. Here, we developed a quantitative microscopy-based protocol to investigate how NTT influences αS condensate formation, well surface adsorption, and maturation. We found that increasing NTT, which reduces αS hydrophobicity, inhibits condensate sedimentation, enhances surface adsorption, and accelerates maturation. Additionally, by increasing well surface hydrophobicity we decreased αS condensate adsorption, delaying their maturation. Thus, we propose that enhanced adsorption, which increases the condensate surface-to-volume ratio, promotes αS nucleation at the condensate-bulk solution interface, accelerating aggregation. Our research indicates that αS condensate adsorption at cellular surfaces may drive toxic aggregate formation in neurodegeneration.