Aberrant Compartment Formation by HSPB2 Mislocalizes Lamin A and Compromises Nuclear Integrity and Function.


Abstract

Small heat shock proteins (HSPBs) contain intrinsically disordered regions (IDRs), but the functions of these IDRs are still unknown. Here, we report that, in mammalian cells, HSPB2 phase separates to form nuclear compartments with liquid-like properties. We show that phase separation requires the disordered C-terminal domain of HSPB2. We further demonstrate that, in differentiating myoblasts, nuclear HSPB2 compartments sequester lamin A. Increasing the nuclear concentration of HSPB2 causes the formation of aberrant nuclear compartments that mislocalize lamin A and chromatin, with detrimental consequences for nuclear function and integrity. Importantly, phase separation of HSPB2 is regulated by HSPB3, but this ability is lost in two identified HSPB3 mutants that are associated with myopathy. Our results suggest that HSPB2 phase separation is involved in reorganizing the nucleoplasm during myoblast differentiation. Furthermore, these findings support the idea that aberrant HSPB2 phase separation, due to HSPB3 loss-of-function mutations, contributes to myopathy.

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KEYWORDS: congenital myopathy; lamin-A/C; nucleus; phase transition; small HSPs

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