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The intrinsically disordered variable domain from dynamin-related protein 1 promotes liquid–liquid phase separation that enhances dynamin assembly and its interaction with cardiolipin-containing membranes

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Dynamins are an essential superfamily of mechanoenzymes that remodel membranes and often contain a "variable domain"important for regulation. For the mitochondrial fission dynamin, dynamin-related protein 1 (Drp1), a regulatory role for the variable domain (VD) is demonstrated by gain- and loss- of-function mutations, yet the basis for this is unclear. Here, the isolated VD is shown to be intrinsically disordered and undergo a liquid–liquid phase separation under in vitro crowding conditions. MD simulations suggest this liquid-liquid phase separation arises from weak, multivalent interactions similar to other systems involving intrinsically disordered regions. These crowding conditions also enhance binding to cardiolipin, a mitochondrial lipid, which appears to also promote phase separation. Since dynamin-related protein 1 is found assembled into discrete punctate structures on the mitochondrial surface, the inference from the present work is that these structures might arise from a condensed state driven by interactions between VD domains and between cardiolipin and VD. These findings support a model where the variable domain mediates phase separation that enables rapid tuning of Drp1 assembly necessary for fission.

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Keyword-2

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