

Abstract

The compartmentalisation into membrane-bound organelles enabled eukaryotic cells the spatiotemporal organisation of various biological processes. Creation of distinct subcompartments facilitates the simultaneous occurrence of biochemical reactions requiring completely different environments. Additional levels of organisation are accomplished by the formation of functional membrane domains. Prohibitins, as putative membrane scaffolds, define such specialised regions and their importance is highlighted by the embryonic lethality of organisms depleted for these proteins. Belonging to the SPFH-domain family, two homologous proteins exist, Phb1 and Phb2. They assemble into ring-like hetero-oligomers to form a high molecular weight complex within the inner membrane of mitochondria. Despite extensive research, the function of prohibitins remains elusive. Phenotypes observed in the absence of these proteins implied their association with a huge variety of cellular processes.

The present study discovered that prohibitins are essential for cell survival at low temperature, thereby facilitating the employment of a focused screen to identify loss-of-function mutants. This approach established cold-sensitive prohibitin mutants that phenocopy the poor growth of a deletion mutant. Concomitantly, they assemble into high molecular weight complexes under non-permissive conditions, demonstrating that complex formation is not sufficient to guarantee prohibitin function. Consistently, affinity-purification of wild-type and cold-sensitive Phb1 variants identified binding partners specifically interacting with a functional prohibitin, suggesting that binding of interactors is an essential feature of these proteins. Furthermore, a significant decrease in cardiolipin was observed in cells cultured at the non-permissive temperature independent of prohibitin, indicating that the combined reduction of cardiolipin and prohibitins represent a condition that is incompatible with cell viability.

This work places prohibitins at the interface of an organisational network to assist in multiprotein complex assembly, presumably via physical interactions with proteins as well as functional dependence on lipid composition.