Structural and molecular basis of protein quality control in the inner mitochondrial membrane by the prohibitin-mAAA complex

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Mitochondrial respiratory function relies on the careful coordination of expression and assembly of oxidative phosphorylation (OXPHOS) components, which consist of both core mitochondrial-encoded and imported nuclear-encoded components. Our previous study identified a large and highly conserved supercomplex called the prohibitin (PHB)–mAAA (matrix-facing ATPase associated with various cellular activities) complex as a key hub that integrates OXPHOS biogenesis and quality control in mitochondria. Here, we investigate the structure, function, and molecular mechanism of the PHB complex from baker's yeast (*Saccharomyces cerevisiae*) involved in protein quality control of the inner mitochondrial membrane. Our single-particle cryo-electron microscopy structure revealed the assembly of the PHB complex into a ring-like structure consisting of 11 alternating PHB1 and PHB2 heterodimers. Interactome analysis using site-specific chemical crosslinking co-immunoprecipitation followed by mass spectrometry revealed a spatial organization of interactions depending on the sub-compartmental location of the modified PHB residues. Interaction analysis and structural modelling indicated a specific interaction between mAAA proteases and the inside of PHB ring. On the other hand, the outside part of PHB complex interacts with more varied proteins, including protein import components, lipid biogenesis and organization enzymes, and OXPHOS components and assembly factors, indicating its function in linking protein biogenesis and degradation. Furthermore, biochemical analyses demonstrated that PHB acts as a scaffolding structure that prohibits and selectively allows newly imported proteins that are misfolded due to heat stress or orphaned due to assembly defect to be subjected for degradation by mAAA proteases. Overall, these findings demonstrate the key function and mechanistic basis of the prohibitin-mAAA complex that bridges the protein biogenesis processes, which includes import, synthesis, folding, and assembly; and quality control by means of proteolytic degradation in mitochondria.