Abstract

The mitochondrial *m*-AAA protease is a conserved metalloprotease facing the matrix. The human *m*-AAA protease exists as homo-oligomers of AFG3L2 or hetero-oligomers of AFG3L2 and PARAPLEGIN. Neurodegenerative disorders like Hereditary Spastic Paraplegia (HSP) and Spinocerebellar Ataxia (SCA28) are caused due to mutations in *SPG7* and *AFG3L2,* respectively. By aiding the biogenesis and performing the quality control of diverse mitochondrial proteins, the *m*-AAA protease regulates several mitochondrial functions. Characterization of the *m*-AAA protease interactors or substrates provides more information about its functions. In this study, characterization of a known interactor of the *m*-AAA protease, called the ***m*-AAA** protease **I**nteracting **P**rotein **1** (MAIP1) was done. Both MAIP1 and *m*-AAA protease were found to influence the steady state levels of the mitochondrial calcium uniporter regulator protein, EMRE (**E**ssential **MCU** **RE**gulator). Biochemical analysis of EMRE showed the existence of a precursor form (p-EMRE) and a processed mature form (m-EMRE). While the human *i*-AAA protease was shown to degrade p-EMRE, the *m*-AAA protease was shown to degrade m-EMRE. The *m*-AAA protease may also provide a structural support for p-EMRE stability. The processing of p-EMRE into m-EMRE is dependent on the pore forming subunit of calcium uniporter, MCU. MAIP1 and *m*-AAA protease function in collaboration to ensure p-EMRE stability.

In yeast, the *m*-AAA protease is a hetero-oligomer of Yta10 and Yta12 subunits. The putative *m*-AAA protease substrates Ilv2, Pda1 and Ilv5 showed precursor accumulation and a tendency to aggregate in the absence of *m*-AAA protease. The previously identified substrates of the *m*-AAA protease, Qcr8, Sdh4, Atp4, Rip1 and Mba1 were shown to form aggregates in the absence of the *m*-AAA protease, suggesting a role of the *m*-AAA protease in aggregate minimization by quality control of aggregation-prone proteins. Furthermore, the *m*-AAA protease activity was shown to be regulated by the surrounding cardiolipin (CL) environment.