FBS Seminar 2017

Date: 17:00-18:00 on Monday, July 31

Place: 2F Seminar Room, Biosystems Building

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Loss of the i-AAA protease YME1L leads to progressive axonal degeneration and locomotor impairment in mice

Abstract

Homozygous mutation in the gene coding for the mitochondrial i-AAA protease YME1L causes a mitochondriopathy associated with neurological dysfunction in humans. Several neurological diseases have been linked to a failure in mitochondrial proteostasis and mitochondrial network fragmentation. As recently shown in cultured cells and in the adult mouse heart, the two inner mitochondrial membrane metalloproteases YME1L and OMA1 cleave the dynamin-like GTPase OPA1 to balance mitochondrial fusion and fission. The long, unprocessed form of OPA1 (L-OPA1) is sufficient to mediate fusion and preserve cristae morphogenesis, whereas cleavage of L-OPA1 and the subsequent formation of short forms of OPA1 (S-OPA1) limits fusion and promotes mitochondrial fragmentation. The loss of YME1L activates OMA1, triggering stress-induced OPA1 processing and fragmentation of the mitochondrial network, and increasing the susceptibility to cell death. In addition to its role in regulating mitochondrial dynamics, YME1L has been implicated in a number of different processes where it participates in regulatory turnover and fulfills quality control functions by degrading misfolded and damaged proteins. In this study, we establish a novel mouse model lacking YME1L in the nervous system and demonstrate that a loss of YME1L leads to progressive axonal degeneration and locomotor impairment combined with mitochondrial trafficking defects. Surprisingly, our data suggest that these phenotypes are in fact independent of stress-induced OPA1 processing. This study contributes to the understanding of disease mechanisms caused by disturbed mitochondrial proteostasis and provides novel insight into the role of YME1L in neurodegenerative processes.

Recent publications

Wai T, Saita S, Nolte H, Müller S, König T, Richter-Dennerlein R, Sprenger HG, Madrenas J, Mühlmeister M, Brandt U, Krüger M, Langer T. (2016). The membrane scaffold SLP2 anchors a proteolytic hub in mitochondria containing PARL and the i-AAA protease YME1L. ***EMBO rep.***, 17: 1844-1856.

Korwitz A, Merkwirth C, Richter-Dennerlein R, Tröder SE, Sprenger HG, Quirós PM, López-Otín C, Rugarli EI, Langer T. (2016). Loss of OMA1 delays neurodegeneration by preventing stress-induced OPA1 processing in mitochondria. ***J. Cell Biol.***, 212: 157-166.

Host: **Koji Okamoto**, Laboratory of Mitochondrial Dynamics, Graduate School of Frontier Biosciences
Tel: 06-6879-7970 Email: kokamoto@fbs.osaka-u.ac.jp

Note: This seminar will be presented in English.

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