Molecular mechanism of mitochondrial tethering mediated by MFN1

Subject Code: C05

With the support by the National Natural Science Foundation of China, the research team led by Prof. Gao Song (高嵩) from the State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, recently reported the molecular mechanism of mitochondrial tethering by dynamin-related GTPase MFN1 upon GTP binding and hydrolysis, in *Nature* (2017, 542: 372—376).

In most of eukaryotic cells, double-membraned mitochondria undergo continuous fission and fusion processes influenced by metabolic conditions, developmental stages, and environmental stimuli. Fusion enables mitochondria to maintain membrane potential and complement damaged mitochondrial DNAs. Defects in mitochondrial fusion may cause a number of diseases, including neurodegeneration, diabetes and cancer. Mitofusins, belonging to the dynamin superfamily of GTPases, play an important role in this process: they are thought to fuse adjacent mitochondria via orchestrated oligomerization and GTP hydrolysis. However, the molecular mechanisms thereof remain unknown. Humans have two mitofusin analogues, namely MFN1 and MFN2, either of which is able to mediate mitochondrial outer membrane fusion. The Gao team determined crystal structures of engineered human MFN1 containing the GTPase domain and a helical domain in different stages of GTP hydrolysis. The helical domain is composed of four α-helices from widely dispersed sequence regions. By using a tryptophan switch, MFN1 alters the conformation upon loading of GTP at the nucleotide-binding area, which promotes dimerization of GTPase domains in the transition state. This dimerization in turn leads to rearrangement of the catalytic histidine finger that facilitates hydrolysis of GTP. Moreover, the similarity of MFN1 structure with a bacterial-dynamin-like protein implies that domain movements may take place during the GTP turnover cycle. A conserved aspartate trigger was found to possibly participate in this process. Disrupting any of the aforementioned elements abolishes the fusogenic activity of MFN1. Finally, the Gao team proposes a mechanistic model for MFN1-mediated mitochondrial tethering. This study sheds light on the molecular basis of mitochondrial fusion and mitofusin-related human diseases.

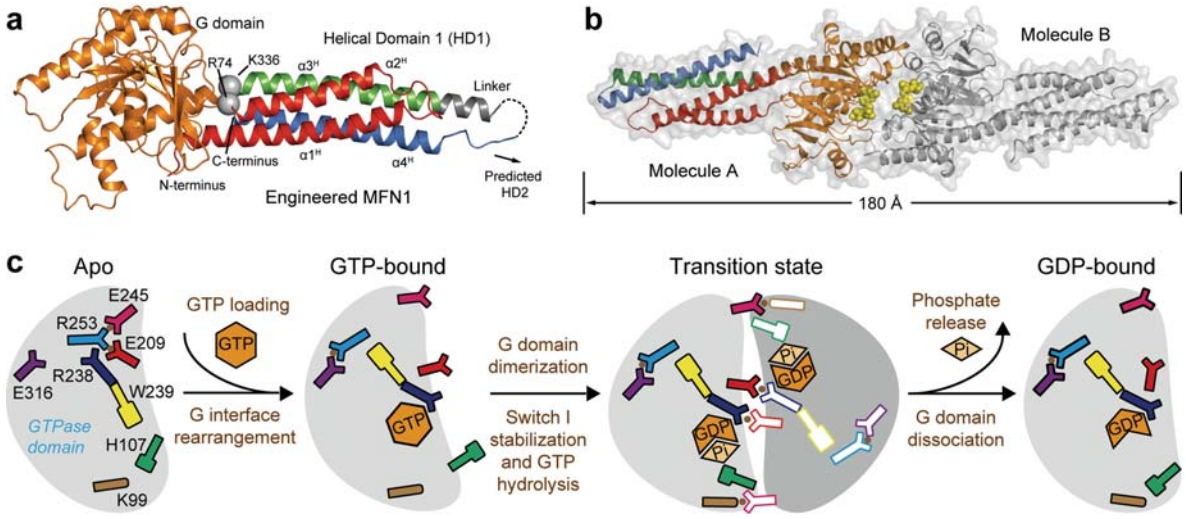

Figure MFN1 mediated mitochondrial tethering. a, Overall structure of engineered MFN1; b, dimerization of GTPase domain in the transition state of GTP hydrolysis; c, conformational rearrangements of MFN1 in the GTP turnover cycle.