Abstract

Coiled-helix-coiled-helix domain containing protein 10 (CHCHD10) is the first mitochondrial protein to be associated with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Although the normal function of D10 remains unknown, numerous pathogenic CHCHD10 mutations have been reported and associated with a wide variety of clinical manifestations ranging from neurological to cardiac diseases. Most mutations have been associated with ALS, FTD, and myopathy, including the S59L mutation, which was the first one to be identified and the most studied to date. To investigate the pathogenic mechanisms of these mutations in vivo, we have generated KO and knock in (KI) mouse models. Mutant S55L (mouse equivalent of human S59L) CHCHD10 KI mice develop protein aggregation in multiple tissues, resulting in proteotoxicity that leads to neurological defects, myopathy, and fatal cardiomyopathy. However, despite the availability of CHCHD10 mouse models, gaps in knowledge remain on the normal function of CHCHD10 (and its paralog protein CHCHD2) and on how mutations affect CHCHD10 protein structure, aggregation, metabolism, and neuronal degeneration in D10 frontotemporal dementia. This presentation will present recent, mostly unpublished findings on the putative functions of CHCHD10, pathogenic mechanisms underlying CHCHD10-pathy, and therapeutic approaches under development.

Publications

