DIPARTIMENTO DI FARMACIA E BIOTECNOLOGIE

Life & Chemical Sciences Seminars

Deciphering OPA1 mutations pathogenicity by combined analysis of mouse and yeast cell models.

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Abstract
OPA1 is mitochondrial dynamin-related GTPase, involved in mitochondrial network dynamic and cristae shaping, energetic efficiency and OXPHOS supercomplexes assembly, mtDNA maintenance and apoptosis control. OPA1 mutations are associated with Dominant Optic Atrophy (DOA), a blinding disease characterized by selective degeneration of retinal ganglion cells, and with its syndromic form DOA "plus", including mitochondrial myopathy with mtDNA deletions. Over 370 OPA1 mutations have been identified so far, although their pathogenicity is not always clear. To investigate the pathogenic mechanism of OPA1 mutations we generated two "ad hoc" cell systems: MGM1/OPA1 chimera yeast model and Opa1-/- MEFs model expressing the mutated human OPA1 isoform 1. We have analyzed one novel and a set of known OPA1 mutations. Yeast model allowed to identify the deleterious effects of mutations and to gain information on their dominance/recessivity. MEFs model enhanced the phenotypic alteration caused by mutations, nicely correlating with the clinical severity observed in patients, and allowed to identify different degrees of severity related to the different mutations. Furthermore, yeast model allowed to perform a high throughput screening of FDA approved molecules, whose efficiency had been then validated in mouse cell models. These two models are therefore complementary, operating in parallel to define the deleterious mechanism and the pathogenicity of novel OPA1 mutations and to test drugs for new therapeutic interventions.

Biosketch
C. Zanna is a cell biochemist with experience in mitochondrial disorders, addressing issues at the cellular biology level. She got the PhD in "Cellular Biology and Physiology" at the Univ. of Bologna in 2005, studying the biochemical alterations in mitochondrial disorders cell models. She moved to National Institutes of Health (NIH), Bethesda, to analyze mitochondrial fusion in Dominant Optic Atrophy (DOA) patients' fibroblasts. From 2005 to 2010 she had a post-doc fellowship at the Univ. of Bologna to investigate the functions of OPA1 protein that is mutated in DOA. Then she worked with Telethon Foundation at the project "Therapeutic strategies to combat mitochondrial disorders". From 2011 to 2012 she had a post-doc fellowship within the European project E-Rare for the study of rare diseases. From 2012 to 2014 she worked at the project "Italian network for MINGIE epidemiology, molecular mechanism and enzyme replacement therapy by stem cell transplant". From 2014 to 2017 she was PI of the FIR project "From yeast to human: how OPA1 isoforms and pathogenic mutations cause neurodegenerations characterized by mtDNA instability" at FABIT, Univ. of Bologna, supported by MIUR. Now, she has a post-doc fellowship at FABIT with the project " Study of neurodegenerations caused by OPA1 mutations by using murine and human cell models".

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