PROGETTO

Supervisore::	Francesca Maltecca
Titolo/*Title*:	Developing novel therapeutic approaches for neurogenerative diseases caused by *AFG3L2* mutations
Curriculum:	Neuroscienze e Neurologia Sperimentale
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://research.hsr.it/en/divisions/neuroscience/mitochondrial-dysfunctions-in-neurodegeneration/francesca-maltecca.html ----------

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

The *m*-AAA proteases, located in the inner mitochondrial membrane (IMM), are hexameric complexes formed by AFG3L2 alone or AFG3L2 and paraplegin. They are crucial components of the quality control system of the IMM and mediate the selective degradation of non-assembled and damaged proteins, thus preserving mitochondrial integrity. [1]

Mutations in *AFG3L2* cause three rare neurodegenerative disorders. In particular, heterozygous mutations in the AFG3L2 proteolytic domain lead to spinocerebellar ataxia type 28 (SCA28), while biallelic mutations in the same domain cause Spastic-Ataxia-Neuropathy Syndrome type 5 (SPAX5). [2] Conversely, mutations in the AFG3L2 ATPase domain are associated with autosomal dominant optic atrophy type 12 (DOA12). [3] This genetic evidence indicates that mutations in diverse domains of AFG3L2 could differently affect its molecular function and determine different clinical outcomes. Currently, there are no available therapies for AFG3L2-related diseases.

Rationale and hypothesis

Previous studies of the lab demonstrated that the absence of AFG3L2 leads to the accumulation of mtDNA-encoded proteins, resulting in impaired respiratory capacity and proteostatic stress. This stress triggers the over-activation of the IMM stress-sensitive protease OMA1, which in turn over-processes the long forms of the IMM fusion protein OPA1 (L-OPA1), leading to mitochondrial fragmentation [2, 4-6].

OMA1 has been recently identified as the pivotal player in communicating mitochondrial stress to the cytosol in experimental cell models. This pathway involves the cleavage of the IMM protein DELE1, which is exported in the cytosol to stimulate HRI-dependent eIF2α phosphorylation, which

elicits the integrated stress response (ISR). [7] The ISR reduces global protein synthesis and drives the expression of cytoprotective genes that allow cells to endure proteotoxic stress (e.g., ATF4). We have recently shown that OMA1-mediated ISR is activated for the first time in the context of a human neurological disease: SPAX5. [8]

Objectives and specific aims

In view of these data, the project aims to:

(i) characterize the mitochondrial endophenotypes that allow molecular discrimination of AFG3L2-related diseases, in particular SPAX5 and DOA12;

(ii) develop new therapeutic approaches specific for these two diseases.

For SPAX5, we will enforce the evidence that pharmacologic potentiation of ISR is beneficial in the *Afg3l2*$^{-/-}$ mouse.

For DOA12, we will test in cell and neuronal models a series of small molecules that we have previously identified by high-content screening (HCS) for their ability to reverse mitochondrial fragmentation, which is the hallmark of this disease.

Expected outcomes

Overall, this project will improve the dissection of the molecular pathways underlying AFG3L2-related diseases and identify candidate molecules that can be further optimized in pre-clinical and clinical settings for the future treatment of SPAX5 or DOA patients.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

Cultural skills: knowledge about neurodegeneration, cerebellar degeneration, optic atrophy, human genetics.

Technical skills: working with cell and animal models, derivation of primary Purkinje neurons, derivation of primary retinal ganglion cells, imaging, molecular biology techniques, biochemistry.

Bibliografia (max. 15)

[1] Quiros at al. Nat Rev Mol Cell Biol. 2015 Jun;16(6):345-59. PMID: 25970558

[2] Tulli et al. J Med Genet. 2019 Aug;56(8):499-511. PMID: 30910913

[3] Baderna et al. Acta Neuropathol Commun. 2020 Jun 29;8(1):93. PMID: 32600459

[4] Maltecca et al. J Neurosci. 2008 Mar 12;28(11):2827-36. PMID: 18337413

[5] Maltecca et al. Hum Mol Genet. 2012 Sep 1;21(17):3858-70. PMID: 22678058

[6] Maltecca et al. J Clin Invest. 2015 Jan;125(1):263-74. PMID: 25485680

[7] Guo et al. Nature. 2020 Mar;579(7799):427-432. PMID: 32132707

[8] Franchino et al. Brain 2024 2024 Mar 1;147(3):1043-1056. PMID: 37804316