

Molecular basis of the Multiple Mitochondrial Dysfunctions Syndrome 2: the pathogenic His96Arg BOLA3 mutation

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Iron-sulfur (Fe/S) clusters are simple inorganic protein cofactors composed by ferrous (Fe²⁺) or ferric (Fe³⁺) iron and sulfide (S²⁻) ions. They are ancient, ubiquitous prosthetic groups, involved in several cellular processes. The clusters biosynthesis and incorporation into scaffold proteins are guaranteed by different biogenesis machineries, specific for each cellular compartment [1-2]. The Fe/S clusters biosynthesis starts in the mitochondrion, where Fe/S proteins take part in important cellular pathways such as oxidative phosphorylation, lipoic acid synthesis and iron metabolism, contributing to the main function of this organelle, which is the production of cellular energy.

Mutations in genes encoding for some components of the mitochondrial ISC machinery, namely NFS1, BOLA3, IBA57, ISCA2 and ISCA1 proteins, lead to a group of rare syndromes which cause autosomal recessive diseases, and which have been identified, since 2011, as Multiple Mitochondrial Dysfunctions Syndromes (MMDS) types 1 to 5. These rare disorders appear early in life with severe weakness, respiratory failure, lactic acidosis, lower energy metabolism and consequent impairment in neurologic development.

Bi-allelic variants in the gene encoding for BOLA3 cause MMDS type 2, which typically appears in early childhood with encephalopathy, leukodystrophy, nonketotic hyperglycinemia, cardiomyopathy, and death [3-4]. A homozygous His96Arg (c. 287 A > G) mutation in the BOLA3 gene involves a fully conserved residue of the bola-like protein family, previously identified as a [2Fe-2S] cluster ligand in the BOLA3-[2Fe-2S]-GLRX5 heterocomplex. The mutation is responsible for severe lactic acidosis and combined respiratory chain complex deficiencies, with the implication of a wide range of organs. The molecular basis of the pathogenicity of the His96Arg mutation have not been investigated yet [5-6].

Here we present the results of the spectroscopic and biochemical characterization of the His96Arg BOLA3 mutant and of its interaction with the partner monothiol glutaredoxin GLRX5, in the formation of BOLA3-[2Fe-2S]-GLRX5 complex. Moreover, we investigated the effect of the mutation on the heterocomplex ability in assembling a [4Fe-4S] cluster on NFS1.

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