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Scientific Paper:

The Faseb Journal 21, 333-344, 2007

Causative role of oxidative stress in a *Drosophila* model of Friedreich ataxia

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Abstract:

Friedreich ataxia (FA), the most common form of hereditary ataxia, is caused by a deficit in the mitochondrial protein frataxin. While several hypotheses have been suggested, frataxin function is not well understood. Oxidative stress has been suggested to play a role in the pathophysiology of FA, but this view has been recently questioned, and its link to frataxin is unclear. Here, we report the use of RNA interference (RNAi) to suppress the *Drosophila* frataxin gene (fh) expression. This model system parallels the situation in FA patients, namely a moderate systemic reduction of frataxin levels compatible with normal embryonic development. Under these conditions, fh-RNAi flies showed a shortened life span, reduced climbing abilities, and enhanced sensitivity to oxidative stress. Under hyperoxia, fh-RNAi flies also showed a dramatic reduction of aconitase activity that seriously impairs the mitochondrial respiration while the activities of succinate dehydrogenase, respiratory complex I and II, and indirectly complex III and IV are normal. Remarkably, frataxin overexpression also induced the oxidativemediated inactivation of mitochondrial aconitase. This work demonstrates, for the first time, the essential function of frataxin in protecting aconitase from oxidative stress-dependent inactivation in a multicellular organism. Moreover our data support an important role of oxidative stress in the progression of FA and suggest a tissue-dependent sensitivity to frataxin imbalance. We propose that in FA, the oxidative mediated inactivation of aconitase, which occurs normally during the aging process, is enhanced due to the lack of frataxin.

Key-words: Frataxin, aconitase, mitochondrial respiration, hyperoxia, RNAi