Mouse and Cellular Models for Friedreich Ataxia: Consequences of Frataxin Deficiency

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Friedreich ataxia (FRDA), the most common recessive ataxia, results from a generalized deficiency of mitochondrial and cytosolic iron-sulfur (Fe-S) protein activity due to a partial loss of function of frataxin, a mitochondrial protein involved in Fe-S cluster (ISC) biosynthesis. Iron-induced oxidative stress and hampered superoxide dismutases signalling have been proposed to be involved in the pathogenesis of the disease. This has led to the use of antioxidants for FRDA therapy. However, to this date, FRDA remains a devastating disease for which there is no cure

We have generated conditional mouse models that reproduce important progressive pathological and biochemical features (cardiac and neuronal) of the human disease, including i) progressive cardiac hypertrophy, ii) progressive ataxia and loss of proprioception, iii) multiple Fe-S dependent enzyme deficiency in affected tissues, iv) time-dependent intramitochondrial iron accumulation. We have used these mouse models for therapeutic testing of different antioxidant compounds. We previously reported that idebenone has a significant effect on the cardiac function and the life-span of the murine model. To further discern the role of oxidative stress in FRDA pathophysiology, we have tested the potential effect of increased antioxidant defense using an MnSOD mimetic (MnTBAP) and Cu,ZnSOD overexpression on the murine FRDA cardiomyopathy. Surprisingly, no positive effect was observed, suggesting that increased superoxide production could not explain by itself the FRDA cardiac pathophysiology. Moreover, we demonstrate that complete frataxin-deficiency does not induce oxidative stress in neuronal tissues nor alters the MnSOD expression and induction in the early step of the pathology (neuronal and cardiac) as previously suggested. We show that cytosolic ISC aconitase activity of IRP-1 progressively decreases while its apo-RNA binding form increases despite the absence of oxidative stress suggesting that in a mammalian system, the mitochondrial ISC assembly machinery is essential for cytosolic ISC biogenesis.

In parallel, in order to identify novel compounds using high-throughput screening technology that may potentially work in combating the disease, we have recently developed a murine fibroblastic model based on antisense strategy using a ribozyme. These cell lines shows highly reduced levels of frataxin reproducing the quantitative defect found in patients and exhibit a proliferation defect, associated with an ISC enzyme deficit. This model is the first stable cellular model for FRDA that shows spontaneous phenotype without exogenous oxidative insult, and is therefore a key model for drug screening.