

Identifying additional sensitive targets in Friedreich ataxia

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Scientific summary

The aim of this project is to identify new targets for the therapy of Friedreich ataxia. This will be done by studying cultured cells in which frataxin-depletion has already been shown to result in the dismantling of the Nrf2-signaling pathway. This central pathway is known to control the expression of a number of crucial genes related to the mitochondria.

We would like first to better understand the underlying mechanism linking frataxin depletion to Nrf2-signaling path dismantling. Second, we wish to better characterize the partner and the different targets of the transcriptional regulation by Nrf2 as to potentially identify new proteins/paths which might be important in the pathophysiology of Friedreich ataxia. The potential specific consequences of affecting each of these targets will be investigated by specific inactivation using shRNAs technology with retroviral infection. As previously done, with idebenone or pioglitazone, we will attempt to pharmacologically counteract the consequences of inactivating each of the identified target either by a rational approach depending on the considered protein/path or by a more general screening using a bank of molecules.

As a result we hope to identify one or more molecules susceptible to be trialled in Friedreich ataxia.

Lay summary

We have been at the origin of two ideas to counteract Friedreich ataxia, namely idebenone in 1997 and pioglitazone in 2005, resulting in a number of clinical trials in the world. We have now delineated a new mechanism in Friedreich ataxia. This mechanism is responsible for the hypersensitivity to oxidative insult observed in case of frataxin depletion. We would like to take advantage of this discovery to identify new targets to counteract the condition.

There are two major aims of this project. Firstly, we want to better understand the consequences of this impaired mechanism (a poor movement in the nucleus of an important factor involved in switching on genes that are essential for mitochondrial function) by studying different cells in culture. This should result in the identification of new and sensitive targets associated with this path. Secondly, using test tube assays



(as with idebenone) or cell cultures (as for pioglitazone), we wish to identify new promising compounds protecting these targets. This might result in new strategies made available for clinicians to counteract Friedreich ataxia.

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