

## FARA- Q&A with Mootha lab

### **1. How did you become involved with FA research?**

The Mootha lab has long been fascinated with all things mitochondria, but until a couple of years ago we had not worked on FA. This changed two years ago, when the lab began to develop a fascination with iron-sulfur clusters and Tom and Karen Hamilton, through the CureFA foundation, made a generous gift to our lab to focus some of our attention on FA. The more we learned about the pathway, the disease and the patients, the more deeply we became engaged and committed to this field.

### **2. What led you to study the effects of oxygen levels on cell and animal models of FA?**

Our lab previously discovered that low oxygen can be beneficial in mouse models of a very different type of mitochondrial disease called Leigh syndrome. But mitochondrial diseases can be very diverse, so we did not know whether other forms of these rare diseases would show similar effects. We thought that FA might be a good candidate because the pathway that's slowed down in FA patients – making iron-sulfur clusters- is an ancient pathway that evolved at a time when there was very little or no oxygen in our planet's atmosphere. We thought that by taking cells back to this "primordial state" of low oxygen, we could boost the pathway.

### **3. What are the key research findings of this published study?**

Frataxin, the gene that's affected in FA, is generally regarded as an essential gene, i.e., if you get rid of it completely, cells cannot function and proliferate. This paper reports the striking and unexpected observation that if we get rid of this gene and then just grow these human cells in very low oxygen concentrations (hypoxia), the cells function and divide just fine. This was also true for entire worms, which usually die without frataxin at room air, but could complete their life cycle and even reproduce without frataxin if grown at low oxygen. We also placed a mouse model of FA in a low oxygen environment, and saw that it didn't develop ataxia to the same extent that mice placed in regular room air did.

This paper goes further to describe the molecular mechanisms and pathways by which low oxygen is benefitting cells lacking frataxin. First, we report that low oxygen directly boosts the activity of the mitochondrial machine that makes iron sulfur clusters. Second, we report that low oxygen causes cells to take up more iron in a form that remains bioavailable (i.e. doesn't "rust" in the cells), and this iron can be used for iron sulfur cluster production. Together, these two mechanisms come together to boost the production of iron sulfur clusters in hypoxia, even in the absence of frataxin.

### **4. Do these results mean that hypoxia could be beneficial for people with FA? Is there anything you would advise people to do or not to do as a result of this research?**

While our results are exciting, it's premature to conclude that hypoxia will be beneficial for patients with FA. First, all of our work to date has been limited to cells, worms, and mice, which of course are not humans. Second, our cellular and animal work has required continuous, severe hypoxia. Oxygen of course is essential for life, and while mild hypoxia can be tolerated by healthy humans, the levels required in these studies can potentially be deadly in humans. At this point, the clinical care and management of patients with FA should not change, and we don't advise FA patients to attempt using hypoxia treatment.

#### **5. What are the next steps to further develop this work?**

We will be performing additional mouse studies to search for alternative means of modulating oxygen in a safe, practical, and effective way. Ideally we will be able to "bottle up" what we've learned from the different mechanisms that hypoxia is activating into a pill that can be tested in animals and then in humans via clinical trials.

#### **6. How should the FA community interpret the findings?**

We hope that the FA community is excited by this basic research – it has cracked open brand-new insights into the relationship between frataxin and oxygen that likely has ancient, evolutionary origins. Additional research in this area could lead to promising new therapies, but we're still not ready for anything in humans.