Low Oxygen May Enhance Energy Production in Patients with Mitochondrial Encephalomyopathies

Oxygen plays the single most important role in the biochemistry and physiology of living creatures. Given this, it would seem counterintuitive that depriving sick cells of oxygen might improve their viability. Yet a hypoxic (low-oxygen) cellular environment may be the very crucible for compelling dysfunctional mitochondria in people with mitochondrial encephalomyopathies to prevent toxicity produced by excess non-used oxygen.

Alba Timon-Gomez, Ph.D., right, with Antonio Barrientos, Ph.D.
The Muscular Dystrophy Association has awarded post-doctoral researcher Alba Timon-Gomez, Ph.D., a development grant to lead a study of how mitochondria in people with mitochondrial encephalomyopathies change and adapt to a low-oxygen environment, so that targets for therapeutic intervention may be identified. Mitochondrial factors that are expressed and responsive to hypoxia may increase efficiency of cellular respiration under hypoxia.

“I’m excited about this grant because it supports our goal of gaining a real understanding of mitochondrial encephalomyopathies, and then finding real targets to combat the impact of the mutation that causes this family of diseases frequently affecting children,” Dr. Timon-Gomez said.

Mutations in the Cells’ Workhorses

Within the cell, mitochondria house the enzymatic systems responsible for making aerobic energy from nutrients: the mitochondrial respiratory chain and the oxidative phosphorylation system. The mitochondrial respiratory chain contains four enzymatic complexes that can dynamically exist as individual entities or combine as supercomplexes. The same mutation in different patients can have distinct biochemical and clinical effects.

Any mutation in this machinery can result in a mitochondrial disease, often impacting the aerobic production of cellular energy within the mitochondria. Since muscles and the brain have major energy needs, they are usually the most affected tissues, causing diseases characterized by muscular dystrophies (myopathies) and neurological problems.
Researchers have shown through preclinical animal models that subjects with these diseases have higher survival rates and milder symptoms under low oxygen levels. A lack of plasticity in the respiratory chain organization is seen in many mitochondrial myopathies. Hypoxic conditions introduce changes in the composition and organization of the respiratory chain to help them more efficiently deliver energy to the major organs and muscles.

An additional benefit is that under hypoxia, fewer reactive oxygen species are produced, which makes for healthier cell function. Finally, under hypoxia, glycolysis is better activated and can partially compensate for the lack of cellular energy.

The Studies in Human Cells

Now, Dr. Timon-Gomez will be studying this process in human cells and specifically looking at the mechanisms of producing two proteins, called HIGD1A and HIGD2A, which have a role in the formation of the respiratory chain in normoxia, and are activated under low oxygen levels.

“Our goal is to understand what regulates respiratory chain plasticity and how this happens,” she said. “Our hypothesis is that these proteins regulate the organization of the DNA multiprotein replication complex (MRC) to allow the cell to adapt their energy production to changing environmental and nutritional conditions – such as hypoxia.”

They have created human cells, both without HIGD1A and HIGD2A, or with an excess of these proteins, to study their importance in energy production and to understand the molecular basis
underlying mitochondrial diseases.

Recently, a higher amount of HIGD1A was shown to promote cell survival in mitochondrial disease models, emphasizing its potential as a therapeutic strategy. The beneficial effects of hypoxia could be mediated by HIGD1A.

“We can’t reasonably tell patients to live in very high altitudes or spend hours a day in a hypoxic chamber. Our hope is that we can work toward targeted therapies that accomplish this without an external hypoxic environment,” Dr. Timon-Gomez said.

Independent Researcher/Principal Investigator

Dr. Timon-Gomez has been working in the lab of mentor Antonio Barrientos, Ph.D., a professor of neurology and biochemistry and molecular biology, who specializes in the study of basic mechanisms that govern the biogenesis of mitochondrial oxidative phosphorylation complexes.

“It was recently shown in preclinical models of mitochondrial disorders that chronic hypoxia regimes have great therapeutic potential,” he said. “Alba is studying key players in the hypoxia therapeutic mechanism, which could be druggable targets in interventions to mimic hypoxia. Such a discovery would be a breakthrough in mitochondrial medicine. This development grant will allow Alba to finish her formation and transition to a faculty position, from which she will continue impacting mitochondrial biology and medicine.”

“Personally, I’m happy that I am leading my first study as a principal investigator,” Dr. Timon-Gomez said. “I am grateful to the MDA for this wonderful opportunity!”