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Effects of iron overload on the mitochondrial genome in patients with thalassemia

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Beta-thalassemia is an inherited anemia caused by a defect in the synthesis of the beta-globin of hemoglobin. For patients with beta-thalassemia major, the severity of the resultant anemia requires routine blood transfusions to prevent morbidity and premature mortality related to the anemia. However, routine blood transfusions lead to progressive iron overload. This undesired consequence puts patients at risk for organ failure such as cirrhosis, heart failure, and diabetes. Knowledge of the molecular mechanisms underlying the relationship between iron overload and organ failure will help guide its management.

A link between iron overload and mitochondrial damage including mitochondrial DNA damage, loss of mitochondrial proteins, and impaired mitochondrial respiration has been described in the literature. Cell culture studies have demonstrated iron overload creates an environment of increased oxidative stress which is known to cause DNA damage. It is plausible that oxidative stress from iron overload causes damage to mitochondrial DNA, in turn compromising cellular and eventually organ function. Results from a pilot study investigating the mitochondrial genome in patients with beta-thalassemia major have found the following abnormalities: mitochondrial genomes had increased rates of the “common” deletion, a biomarker of mitochondrial DNA damage, and also decreased copies of mitochondrial genomes per cell when compared with healthy control patients. These results suggest damage to mitochondrial DNA may be help explain clinical iron toxicity in patients with beta-thalassemia major.

We propose to further investigate the relationship between iron overload and mitochondrial DNA damage in a larger group of well-characterized patients with beta-thalassemia major. Clinical measures of iron overload and iron toxicity will be correlated with mitochondrial DNA damage, specifically the frequency of the “common” deletion and mitochondrial genome copy number per cell. The utility of these metrics as biomarkers of iron toxicity that precedes organ damage will be studied. Mitochondrial DNA damage will be further investigated in a novel manner with next-generation sequencing. Use of these techniques will allow quantification of mitochondrial DNA mutations and the discovery of novel mutations. In addition, the relationship between iron overload and mitochondrial DNA damage as well as mitochondrial function will be investigated through the use of cell culture experiments.