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Ironing out the links between iron, mitochondria and disease.

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X-linked sideroblastic anemia with ataxia (XLSA/A2), is an incurable heterogeneous nonprogressive neurodevelopmental disorder. Mutations in *ABCb7*, a gene encoding a mitochondrial transport protein involved in biogenesis of iron sulfur clusters (ISC), underlie the disease. ISC are import co-factors, intimately involved in the chemical reactions that power the cell, repair DNA and create new proteins.

XLSA/A2 sees all of these processes disrupted to some extent but the chain of cause-and-effect is difficult to unravel. Despite the importance of ISCs biology, the tools available to study these species *in situ* are limited. To understand how mutations in *ABCb7* disrupt ISC metabolism and injure the cell we need tractable biochemical models that retain elements of iron-sulfur biology salient to man. Fortunately, *Caenorhabditis elegans* is ideally suited to this task. By deploying X-ray micro-imaging and micro-analysis we have analyzed the chemistry of iron within intact, fully hydrated *C. elegans*. These data highlighted accumulation of inappropriate iron-sulfur species within the mitochondria upon disruption to *abtm-1* (the nematode ortholog of *ABCb7*). This deleterious process drives dysfunction, accelerates age-related loss of mitochondrial ISC synthetic capacity and fosters mitochondrial dysfunction. The cycle of mitochondrial iron accumulation seen in XLSA/A2 recapitulates aspects of dysfunction observed across a range of diseases, including Fredrich's ataxia. The gatekeeper role played by ABCB7's is unique but poorly characterized.

Coupling versatility of *C. elegans* models with micro-analytical techniques afford unprecedented opportunities to study ill-defined aspects of mitochondrial iron biology. The relevance of these findings and applicability of the approach to other diseases will be discussed.

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