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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 Friedreich'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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