BEC preprints 2026.13
https://doi.org/10.26124/becprep2026-0013
Open Access

Iron as a Central Regulator of Mitochondrial Function and Systemic Energy Metabolism

Günter Weiss, Chiara Volani

Department of Internal Medicine II, Innsbruck Medical University, Anichstr. 35, A-6020 Innsbruck Guenter.weiss@i-med.ac.at

Contribution to MiP2026 – **Received** 2026-09-29 – **Online** 2026-10-08

Cite: Weiss G, Volani C (2026) Iron as a Central Regulator of Mitochondrial Function and Systemic Energy Metabolism. BEC preprints 2026.13 https://doi.org/10.26124/becprep2026-0013

Summary

Iron is central to mitochondrial energy metabolism through its incorporation into haem and iron–sulfur clusters required for electron transport, the TCA cycle and oxidative phosphorylation. Mitochondrial iron availability also interacts with oxygen sensing, redox balance and intermediary metabolism. Conversely, mitochondrial activity influences iron demand and homeostasis. These interactions are particularly relevant in heart and skeletal muscle, where iron status, oxygen delivery and mitochondrial capacity collectively influence ATP production, exercise performance and tissue function but also for general aspect of metabolism, cell multiplication and immune function.

Iron, mitochondria and secondary metabolic processes

Iron is both an essential micronutrient and a potentially toxic redox-active metal. Its importance to mitochondrial biology arises principally from its incorporation into haem and iron–sulfur (Fe-S) clusters, which support oxidative phosphorylation, intermediary metabolism and cellular redox regulation. Mitochondria are consequently not merely consumers of iron but major sites of iron utilization and iron containing co-factor biosynthesis(1).

Cytoplasmic iron enters mitochondria predominantly through the mitoferrin transporters MFRN1 and MFRN2. Once in the mitochondrial matrix, it can be incorporated into Fe-S clusters, used for haem synthesis, or stored in mitochondrial ferritin. Fe-S cluster assembly requires a conserved machinery involving NFS1, ISCU, frataxin and GLRX5, whereas mitochondrial haem synthesis culminates in ferrochelatase-mediated insertion of Fe^{2+} into protoporphyrin IX. Iron export from mitochondria is done via GLRX5 and ABCB7 in the context of Fe-S cluster biosynthesis. Haem is exported from mitochondria to the cytoplasm through FLVCR1b or TANGO2. Whether molecular iron is exported by mitochondrial remains elusive(1, 2).

The consequences for mitochondrial energy metabolism are substantial. Fe-S centers participate directly in respiratory-chain complexes I–III and in electron

transfer from fatty-acid oxidation through electron-transfer flavoprotein dehydrogenase. Complex II also contains several Fe-S centers. Consequently, iron availability influences the ability of mitochondria to oxidize carbohydrates, fatty acids and amino acids and to convert their reducing equivalents into ATP. Additionally, the tricarboxylic-acid (TCA) cycle is dependent on cellular iron availability. Mitochondrial aconitase contains a [4Fe-4S] cluster and catalyses the conversion of citrate to isocitrate. The translational expression of mitochondrial aconitase is controlled by interaction of iron regulatory proteins (IRPs) with a RNA stem loop structure in the 5' untranslated region of mitochondrial aconitase mRNA, known is iron response element (IRE)(3). Limited iron availability activate IRPs which then repress m-aconitase translation, TCA activity, NADH formation and subsequently mitochondrial ATP production, whereas iron abundance de-activate IRPs and enforce TCA cycle and mitochondrial activity(4). In addition, succinate dehydrogenase, catalysing the oxidation of succinate to fumarate and FADH2 also contains several iron -sulfur clusters, also connecting iron driven TCA activity to mitochondrial oxidative capacity with FADH2 formation(1, 2).

Iron therefore connects mitochondrial respiration to several secondary metabolic processes (Table 1). Haem is required not only for respiratory cytochromes but also for haemoglobin and myoglobin synthesis, linking mitochondrial iron metabolism to systemic and cellular oxygen transport. Iron-dependent enzymes also regulate oxygen sensing: prolyl hydroxylase domain (PHD) enzymes require Fe^{2+} and O_2 to hydroxylate hypoxia-inducible factor (HIF), thereby coupling iron availability to transcriptional responses to tissue oxygenation. (5, 6). Iron deficiency can consequently alter metabolism even before severe anaemia develops(7, 8)

Conversely, mitochondrial activity feeds back on iron metabolism. Increased respiratory activity raises demand for Fe-S clusters and haem, while electron leakage and reactive oxygen species (ROS) can damage Fe-S proteins and alter iron handling. Excess labile mitochondrial iron can itself promote oxidative damage through iron-catalysed radical reactions and lipid peroxidation(1, 2). Thus, mitochondrial iron homeostasis represents a balance between iron-dependent metabolic capacity and iron-mediated oxidative toxicity.

Physiological and pathological context

The interaction between iron and mitochondria becomes particularly important in tissues with high energetic and oxygen demands, notably heart and skeletal muscle. Cardiomyocytes rely heavily on mitochondrial oxidative phosphorylation to sustain continuous contraction. Direct analysis of human failing hearts has demonstrated lower myocardial iron concentrations in heart failure, accompanied by alterations in mitochondrial respiration and respiratory-chain metabolism(9). Experimental and clinical data suggests that myocardial iron deficiency can contribute to impaired energetic reserve, although systemic iron deficiency, anaemia, inflammation and mitochondrial iron sequestration may coexist and should not be considered equivalent phenomena(10, 11).

Skeletal muscle provides another important example(12-14). During exercise, cellular energy demand increases dramatically and mitochondrial oxidative

phosphorylation must increase accordingly. Iron deficiency can impair this response through effects on respiratory-chain components, haem-containing proteins and oxygen delivery(15) while iron overload may exert tissue damaging effects and result in contractile dysfunction. Of importance, cardiomyocyte iron import is controlled by the divalent metal transporter DMT1 and its pharmacological modulation can preserve cardiomyocyte functionality(16, 17). Of interest, iron fluxes are linked to cellular calcium fluxes because L-type calcium channels can transport iron whereas calcium antagonists such as nifedipine reverse cellular iron loading via DMT1(18, 19). However, human studies indicate that the relationship is more complex: reduced exercise capacity in iron-deficient individuals may arise from impaired oxygen transport, altered central cardiovascular responses, or tissue-specific metabolic effects rather than from an intrinsic mitochondrial defect alone(12, 20).

Exercise also modifies iron homeostasis. Repeated or strenuous exercise increases inflammatory signaling and hepatic hepcidin production, which reduces intestinal iron absorption and iron release from storage cells(21). In athletes, recurrent exercise-induced hepcidin responses can therefore contribute to functional iron deficiency even when total body iron stores are not profoundly depleted. A 2024 study of 1,190 athletes found iron deficiency in approximately 20%, although the relationship between iron status and performance remains heterogeneous(22).

Finally, iron and oxygen form a tightly interconnected regulatory system. Iron is required for hemoglobin, myoglobin, cytochromes and oxygen-sensing enzymes, while oxygen availability influences iron trafficking and HIF signaling. This creates a physiological feedback network in which oxygen delivery, mitochondrial oxidative capacity, iron availability and metabolic substrate utilization continually influence one another. Pathological disruption at any point—including iron deficiency, inflammation, hypoxia, mitochondrial iron overload or excessive ROS production—can therefore propagate through the system.

In summary, mitochondrial iron metabolism is best viewed not as an isolated micronutrient pathway but as a central metabolic hub. Adequate iron enables electron transport, TCA-cycle activity, haem synthesis and oxygen sensing; excessive or poorly controlled iron promotes oxidative injury. The resulting iron–mitochondria–oxygen axis is particularly consequential in the heart and skeletal muscle, where mitochondrial ATP production and oxygen delivery determine functional performance.

References:

1. Galy B, Conrad M, Muckenthaler M. Mechanisms controlling cellular and systemic iron homeostasis. Nat Rev Mol Cell Biol. 2024;25(2):133-55.
2. Rouault TA, Maio N. Biogenesis and functions of mammalian iron-sulfur proteins in the regulation of iron homeostasis and pivotal metabolic pathways. J Biol Chem. 2017;292(31):12744-53.
3. Schalinske KL, Chen OS, Eisenstein RS. Iron differentially stimulates translation of mitochondrial aconitase and ferritin mRNAs in mammalian cells. Implications for iron

regulatory proteins as regulators of mitochondrial citrate utilization. J Biol Chem. 1998;273(6):3740-6.
4. Oexle H, Gnaiger E, Weiss G. Iron-dependent changes in cellular energy metabolism: influence on citric acid cycle and oxidative phosphorylation. Biochim Biophys Acta. 1999;1413(3):99-107.
5. Haase VH. Hypoxic regulation of erythropoiesis and iron metabolism. Am J Physiol Renal Physiol. 2010;299(1):F1-13.
6. Peyssonnaux C, Zinkernagel AS, Schuepbach RA, Rankin E, Vaulont S, Haase VH, et al. Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). J Clin Invest. 2007;117(7):1926-32.
7. Volani C, Paglia G, Smarason SV, Pramstaller PP, Demetz E, Pfeifhofer-Obermair C, et al. Metabolic Signature of Dietary Iron Overload in a Mouse Model. Cells. 2018;7(12).
8. Fischer C, Valente de Souza L, Komlodi T, Garcia-Souza LF, Volani C, Tymoszuk P, et al. Mitochondrial Respiration in Response to Iron Deficiency Anemia: Comparison of Peripheral Blood Mononuclear Cells and Liver. Metabolites. 2022;12(3).
9. Chang HC, Shapiro JS, Ardehali H. Getting to the "Heart" of Cardiac Disease by Decreasing Mitochondrial Iron. Circ Res. 2016;119(11):1164-6.
10. Lemieux H, Semsroth S, Antretter H, Hofer D, Gnaiger E. Mitochondrial respiratory control and early defects of oxidative phosphorylation in the failing human heart. Int J Biochem Cell Biol. 2011;43(12):1729-38.
11. Molina AJA, Gnaiger E, Kitzman DW. Mitochondrial Respiration and Exercise Performance in Patients With Heart Failure With Preserved Ejection Fraction-Reply. JAMA Cardiol. 2023;8(11):1101-2.
12. Scandalis L, Kitzman DW, Nicklas BJ, Lyles M, Brubaker P, Nelson MB, et al. Skeletal Muscle Mitochondrial Respiration and Exercise Intolerance in Patients With Heart Failure With Preserved Ejection Fraction. JAMA Cardiol. 2023;8(6):575-84.
13. McLane JA, Fell RD, McKay RH, Winder WW, Brown EB, Holloszy JO. Physiological and biochemical effects of iron deficiency on rat skeletal muscle. Am J Physiol. 1981;241(1):C47-54.
14. Thompson CH, Green YS, Ledingham JG, Radda GK, Rajagopalan B. The effect of iron deficiency on skeletal muscle metabolism of the rat. Acta Physiol Scand. 1993;147(1):85-90.
15. Leermakers PA, Remels AHV, Zonneveld MI, Rouschop KMA, Schols A, Gosker HR. Iron deficiency-induced loss of skeletal muscle mitochondrial proteins and respiratory capacity; the role of mitophagy and secretion of mitochondria-containing vesicles. FASEB J. 2020;34(5):6703-17.
16. Rhee JW, Yi H, Thomas D, Lam CK, Belbachir N, Tian L, et al. Modeling Secondary Iron Overload Cardiomyopathy with Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes. Cell Rep. 2020;32(2):107886.
17. Papingiotis G, Mantzourani M, Gogas H, Filippatos G, Farmakis D. Iron overload cardiomyopathy. Heart Fail Rev. 2026;31(1).
18. Ludwiczek S, Theurl I, Muckenthaler MU, Jakab M, Mair SM, Theurl M, et al. Ca(2+) channel blockers reverse iron overload by a new mechanism via divalent metal transporter-1. Nat Med. 2007;13(4):448-54.
19. Oudit GY, Sun H, Trivieri MG, Koch SE, Dawood F, Ackerley C, et al. L-type Ca2+ channels provide a major pathway for iron entry into cardiomyocytes in iron-overload cardiomyopathy. Nat Med. 2003;9(9):1187-94.
20. van der Meer P, van der Wal HH, Melenovsky V. Mitochondrial Function, Skeletal Muscle Metabolism, and Iron Deficiency in Heart Failure. Circulation. 2019;139(21):2399-402.

21. Tobiasch AK, Dunnwald T, Adami PE, Garrandes F, Bermon S, Brunelli L, et al. Long-distance trail running induces functional iron deficiency driven by inflammation. Blood Adv. 2026;10(17):5836-46.
22. Keller K, Friedrich O, Treiber J, Quermann A, Friedmann-Bette B. Iron deficiency in athletes: Prevalence and impact on VO(2) peak. Nutrition. 2024;126:112516.

Copyright ©2026 The author. This is an Open Access preprint (not peer-reviewed) distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. © The author, who has granted BEC preprints an Open Access preprint license in perpetuity.