Introduction to Metals in Biology 2017: Iron transport, storage, and the ramifications

Published, Papers in Press, June 14, 2017, DOI 10.1074/jbc.R117.801332

F. Peter Guengerich[1]

From the Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-0146

Edited by Chris Whitfield

In this tenth Thematic Series in Metals in Biology, six Minireviews deal with aspects of iron metabolism. A number of important proteins control iron homeostasis, including hepcidin and ferroportin, in various cells. Other aspects of iron dealt with here include biogenesis of iron–sulfur proteins and chaperones that deliver iron cofactors in cells. Additionally, an iron-regulated metastasis suppressor interacts with the epidermal growth factor receptor and mediates its downstream signaling activity.

Our tenth Thematic Series in Metals in Biology (1–9) deals with a popular metal, iron, which has myriad functions in biological systems. This transition metal has properties that allow for useful coordination, for use as a Lewis acid, and for redox capacity. However, it also has detrimental roles in oxygen toxicity, and its free cellular concentrations are tightly regulated. Disease states are known with both iron deficiency and iron overload (10).

The first Minireview, by Coffey and Ganz (11), deals with hepcidin, the master regulator of iron homeostasis in mammals. Uptake of iron involves divalent metal ion transporter 1 (DMT1), ZRT/IRT-like protein 8 (ZIP8), and ZIP14. The lone mammalian cellular exporter of iron is ferroportin. Heme transport involves other systems. Other elements are involved in cellular and systemic iron regulation, and iron homeostasis is a complex endocrine and paracrine system.

The second Minireview, by Knutson (12), also deals with the transport of iron in mammalian systems. Differences among cells are emphasized, including duodenal enterocytes, erythrocyte precursors, macrophages, and hepatocytes. The Minireview expands on DMT1, ferroportin, and other proteins, *e.g.* transferrin and ZIP14.

Our third and fourth Minireviews (by Rouault and Maio (13) and by Braymer and Lill (14)) deal with another topic, the biogenesis and roles of mammalian iron–sulfur proteins that are involved in iron homeostasis. A focus of the Minireview of Rouault and Maio (13) is on mammalian cytosolic aconitase, also known as iron regulatory protein 1 (IRP1), and its homologue, iron regulatory protein 2 (IRP2). IRP1, which is related to the well-known mitochondrial aconitase involved in the tricarboxylic acid cycle, uses its Fe–S cluster in sensing and regulating cellular iron homeostasis. Iron-responsive elements (IREs) are involved in the action of the IRPs. The synthesis and delivery of the Fe–S clusters is discussed. The Minireview by Braymer and Lill (14) is focused on the biosynthesis of Fe–S clusters *per se* in mammalian systems, with a focus on assembly in mitochondria. Featured here are the scaffold Isu1 and the trafficking protein Grx5. Other important players are the cysteine desulfurase Nfs1, the allosteric regulatory protein Yfh1 (frataxin), the ferredoxins (yeast) Yah1 and (human) FDX2, and the Hsp70 chaperone Ssq1 and co-chaperone Jac1 (14).

The delivery of iron cofactors is further elaborated in our fifth Minireview, written by Philpott *et al.* (15). Cytosolic iron chaperones include poly(r(C))-binding proteins (PCBPs), which facilitate the metalation of ferritin and some non-heme iron enzymes. Nuclear co-activator 4 (NCOA4) reverses this process by directing ferritin to autophagosomes for degradation and iron release. Glutaredoxin–BolA complexes serve as chaperones for iron–sulfur cluster trafficking in the cytosol.

The remaining Minireview in this series is by Menezes *et al.* (16). This Minireview focuses on iron-regulated metastasis suppressor, N-Myc downstream-regulated gene 1 (NDRG1), which inhibits the expression of the epidermal growth factor receptor (EGFR). NDRG1 inhibits pro-oncogenic EGFR and is of clear relevance in tumor biology. NDRG1 acts as a metastasis suppressor in a variety of tumors and is regulated via hypoxia-inducible factor-1α (HIF1α)-dependent and -independent mechanisms.

Thus, we see that the regulation of the homeostasis of iron is a complex matter in mammalian cells. As pointed out in one of the Minireviews, the transport and metabolism of heme-bound iron are even more complex (15). The significance of the metal iron in biology is underscored by the plethora of systems to control it. It is humbling to note that iron is only one of the metals essential to life and that similarly complex systems are also in place for copper, zinc, and other important metals.

I hope that you will enjoy reading these Minireviews. The next Thematic Series on Metals in Biology will deal with aspects of copper and is scheduled to be published in early 2018.

Acknowledgments—Thanks are extended to K. Trisler for assistance in preparing the manuscript and to the authors of the individual Minireviews, who reviewed a draft for accuracy.

The author declares that he has no conflicts of interest with the contents of this article.

[1] To whom correspondence should be addressed: Dept. of Biochemistry, Vanderbilt University School of Medicine, 638B Robinson Research Bldg., 2200 Pierce Ave., Nashville, TN 37232-0146. Tel.: 615-322-2261; Fax: 615-343-0704; E-mail: f.guengerich@vanderbilt.edu.

References

1. Guengerich, F. P. (2009) Thematic Series: Metals in Biology. *J. Biol. Chem.* **284,** 709
2. Guengerich, F. P. (2009) Thematic Minireview Series: Metals in Biology. *J. Biol. Chem.* **284,** 18557
3. Guengerich, F. P. (2010) Thematic Minireview Series: Metals in Biology 2010. *J. Biol. Chem.* **285,** 26727
4. Guengerich, F. P. (2012) Thematic Minireview Series: Metals in Biology 2012. *J. Biol. Chem.* **287,** 13508–13509
5. Guengerich, F. P. (2013) Thematic Minireview Series: Metals in Biology 2013. *J. Biol. Chem.* **288,** 13164
6. Guengerich, F. P. (2014) Thematic Minireview Series: Metals in Biology 2014. *J. Biol. Chem.* **289,** 28094
7. Guengerich, F. P. (2015) Introduction: Metals in Biology: Metals at the host-pathogen interface. *J. Biol. Chem.* **290,** 18943–18944
8. Guengerich, F. P. (2015) Introduction: Metals in Biology: α-Ketoglutarate/iron-dependent dioxygenases. *J. Biol. Chem.* **290,** 20700–20701
9. Guengerich, F. P. (2016) Metals in Biology 2016: Molecular basis of selection of metals by enzymes. *J. Biol. Chem.* **291,** 20838–20839
10. Tokar, E. J., Boyd, W. A., Freedman, J. H., and Waalkes, M. P. (2013) Toxic effects of metals. in *Casarett and Doull's Toxicology: The Basic Science of Poisons* (Klaassen, C. D. ed), 8th Ed., pp. 981–1030, McGraw-Hill, New York
11. Coffey, R., and Ganz, T. (2017) Iron homeostasis: an anthropocentric perspective. *J. Biol. Chem.* **292,** 12727–12734
12. Knutson, M. D. (2017) Iron transport proteins: gateways of cellular and systemic iron homeostasis. *J. Biol. Chem.* **292,** 12735–12743
13. Rouault, T. A., and Maio, N. (2017) Biogenesis and functions of mammalian iron–sulfur proteins in the regulation of iron homeostasis and pivotal metabolic pathways. *J. Biol. Chem.* **292,** 12744–12753
14. Braymer, J. J., and Lill, R. (2017) Iron–sulfur cluster biogenesis and trafficking in mitochondria. *J. Biol. Chem.* **292,** 12754–12763
15. Philpott, C. C., Ryu, M.-S., Frey, A. G., and Patel, S. (2017) Cytosolic iron chaperones: proteins delivering iron cofactors in the cytosol of mammalian cells. *J. Biol. Chem.* **292,** 12764–12771
16. Menezes, S. V., Sahni, S., Kovacevic, Z., and Richardson, D. R. (2017) Interplay of the iron-regulated metastasis suppressor NDRG1 with epidermal growth factor receptor (EGFR) and oncogenic signaling. *J. Biol. Chem.* **292,** 12772–12782