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Thematic Minireview Series: Metals in Biology 2010*

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Metals are present in nearly one-half of protein structures analyzed to date and play important roles in many of these enzymes. This prologue introduces the third of the Thematic Minireview Series on Metals in Biology, which is focused on iron homeostasis. The four minireviews in the current series deal with redox cycling in iron metabolism, the biogenesis and assembly of iron-sulfur centers (two articles), and the assembly of iron into heme.

Metals are very important in biochemistry, even though they are not considered as a table of contents heading, etc., in the sense of carbohydrates, lipids, RNA, etc. Recent surveys of three-dimensional structures of enzymes indicate that 47% require metals and 41% contain metals in their catalytic centers (1, 2). Metals, as superacids, can increase the electrophilicity or nucleophilicity of reacting species, increase the acidity of a reacting species, and promote heterolysis (1). They also function as redox centers, carry oxygen, and use their abilities to bind ligands to act as molecular "switches" in signal transduction. Two previous Thematic Minireview Series on Metals in Biology dealt with biochemical aspects of a variety of metals, including iron, copper, selenium, nickel, vanadium, and arsenic (3, 4). In this third series, the focus is on research in the area of iron homeostasis, which is important because of the prominence of this transition metal in so many processes in biochemistry.

The first minireview, by Daniel J. Kosman, deals with redox cycling in iron uptake, efflux, and trafficking. The balance between ferric and ferrous iron is delicate and, if not tightly controlled, can lead to undesirable consequences in terms of oxidative stress to cells. Ferrireductases (Fe^{3+} reductases) and ferroxidases (Fe^{2+} oxidases) are involved. Some of the processes also involve another transition metal, copper, and are understood to be involved in serious genetic disorders in humans. Studies with microorganisms also have revealed general roles for these processes in aerobic organisms.

The next two minireviews deal with aspects of the formation of iron-sulfur clusters in mitochondria and cytosol. Timothy L. Stemmler and co-workers discuss the role of the mitochondrial protein frataxin. The scaffold protein Isu is utilized in the process and interacts with free (ferrous) iron, a cysteine desulfurase that provides sulfide, and the protein frataxin, which is produced in the ribosomes and targeted to mitochondria. The inherited neurodegenerative disease Friedreich ataxia is the result of frataxin deficiency. Whether frataxin functions as a chaperone or a regulator element is still unclear. Anil K. Sharma and co-workers review cytosolic iron-sulfur cluster assembly, which is also important and complex. The cytosolic iron cluster assembly system involves scaffolds, chaperones, electron transfer, sulfide generation, and proteins involved in iron-sulfur protein transport and export. This process is involved in overall iron regulation and in the synthesis of numerous important iron-sulfur proteins.

The fourth minireview in this series, by Iman J. Schultz and co-workers, deals with iron and porphyrin trafficking in heme biogenesis. Free iron is regulated and made available for incorporation into heme. In turn, heme transport also is highly regulated, and several proteins may be involved. In addition, there are dietary sources of heme and systems that can utilize this in terms of transport. Finally, heme and free iron generated from heme destruction can be recirculated in the body.

Overall, the processes described in this thematic minireview series show the complexity of dealing with a single metal, iron. This series should convey much of the current state of the field and its relevance to human disease as well as basic biology. I thank Dr. Kosman for suggestions in this area. Again, this is the third of these Thematic Minireview Series on Metals in Biology, and additional minireviews in this area will deal with other interesting aspects of more metals.

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* This minireview will be reprinted in the 2010 Minireview Compendium, which will be available in January, 2011.

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