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Preface

Transferrins: Molecular mechanisms of iron transport and disorders

Iron is an essential trace metal for all living organisms with the exception of a few members of the *genus Lactobacillus* and some strains of *Bacillus*. Despite its abundance and special chemical properties, iron acquisition by all living organisms presents major challenges. On the one hand, the easy inter-conversion between ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions makes iron an attractive transition metal for many biological redox processes. On the other hand, reduced iron or "free" iron in the cell has the propensity to generate highly reactive oxygen species such as hydroxyl radicals which can damage cellular components including lipid membranes, nucleic acids and proteins. To maintain the balance between iron as an essential nutrient and iron as a potential cytotoxin, living organisms have developed well orchestrated homeostatic mechanisms to regulate the absorption, transport, storage and mobilization of iron both at the cellular and systemic levels.

Recent discoveries of major protein players affecting iron homeostasis such as the divalent metal transporter 1 (DMT1), the duodenal cytochrome b (Dcytb), hephaestin (Hp), ferroportin-1 (FPN1), hemojuvelin (HJV) and hepcidin emphasize the complex nature of iron metabolism. The biochemistry of iron, its uptake and utilization within the cell are incompletely understood and will likely be topics of research for many years to come. Given these new findings, the paradoxical nature of iron (abundant but poorly available) and the catastrophic consequences of iron imbalance, it is timely to dedicate a special issue to highlight recent advances in our understanding of the transport of iron and the mechanisms that control and regulate cellular iron metabolism. This special volume is divided into seven sections encompassing the history of iron homeostasis and diseases of iron imbalance, the X-ray structure of the transferrins, the transferrin family members and transferrin receptors, the anions and iron uptake, transport, and release mechanisms, non-transferrin bound iron and other aspects of transferrin structure–function relationships.

Transferrins (Tf) are single-chain glycoproteins containing on average 700 amino acids with a molecular mass of ~80 kDa. The similarity between X-ray crystal structures among transferrin family members across all species is not surprising given the 60–80% sequence identity. In vertebrates, the major protein involved in the delivery of transferrin containing iron into cells is the plasma membrane transferrin receptor (TfR). Two types of TfR, TfR1 and TfR2 are known with TfR1 being the widely expressed and the best-characterized of the two receptors. TfR1 is a homodimeric membrane glycoprotein of molecular mass ~190,000 Da that binds two molecules of transferrin in a pH dependent manner and allows delivery of iron into cells. Once in the cytosol, iron is either immediately utilized or stored in ferritin for later use. Virtually all cells, except mature red blood cells, have this receptor on their surface, but it is particularly abundant in the erythron, placenta and liver. Following the release of iron, the transferrin/transferrin receptor complex (Tf/TfR1) is recycled back to the cell surface where it dissociates at the higher pH value of blood (~pH 7.4). It has been estimated that transferrin is recycled between 100 and 200 times during its lifetime. Although, internalization of Tf-bound iron is the predominant pathway of iron uptake by cells under normal circumstances, compelling evidence in the literature suggest alternative mechanisms of iron uptake including non-Tf-bound iron transporters, divalent metal transporter 1 (DMT1), calcium channels, H-chain ferritin receptors, senescent red blood cells, and others.

Since their discovery over six decades ago, the transferrins have attracted much scientific interest due to their ability to reversibly bind and release a variety of metal ions. Ground-breaking structural work in the early 80s has defined much of the chemical nature of the high affinity binding sites and has provided insight into the mechanisms of the binding and release of metal ions, particularly iron. Many intensive studies have followed and were aimed towards a deeper understanding of these unique iron-binding proteins, the transferrin/transferrin receptor mediated cellular iron uptake pathway and the strategies that exploit the Tf/TfR complex as a drug carrier system. The determination of the structure of the transferrin receptor 1 (TfR1), the identification of the mutations in the HFE gene responsible for hereditary hemochromatosis, and the discoveries of new players affecting iron homeostasis have provided new insights into the complex metabolic pathways for iron.

The twenty-four papers constituting this special volume have been written by experts in the field of iron metabolism who have contributed seminal findings to the field. This collection of papers brings together, in a concise yet comprehensive manner, our current knowledge of how living organisms deal successfully with the problem of efficient transport and acquisition of iron. The reviews, recent findings and new insights contained in this special volume should serve as an important resource for researchers in the future but also as an inspiration for young scientists interested in pursuing studies in the field of iron biochemistry and metabolism.

Fadi Bou-Abdallah is an assistant professor of chemistry at the State University of New York (SUNY) at Potsdam. He received his M.Sc. in Chemistry in 1996 from the Lebanese University, Lebanon and his Ph.D. in Physical Chemistry in 2000 from the University of Paris-7, France. He then moved to the United States to work as a postdoctoral fellow with Professor N. Dennis Chasteen at the University of New Hampshire where he received the "Excellence in Research Award" in recognition of his exemplary contributions to the research enterprise of the University. He was later appointed as a research scientist in the Chemistry department at UNH where he studied the structure–function relationships of a number of metalloproteins, in particular those proteins involved in the metabolism of iron, i.e. ferritin and transferrin. At present,

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his research interests are in the general area of iron–protein biochemistry, part of a major international effort to understand the role of iron in health and disease. He is the author of numerous publications and serves on the editorial board of Biochimica Biophysica Acta, General Subjects (BBAGEN), the Mediterranean Journal of Chemistry (Med. J. Chem.), and Bioenergetics Open Access – OMICS Publishing Group. He is a member of the American Chemical Society (ACS), the International BioIron Society (IBIS), the Council on Undergraduate Research (CUR) and Sigma Xi Honor Society. He also serves as a reviewer to NSF and to over a dozen of international scientific journals. He is the recent recipient of several awards including grants from Research Corporation and NSF for his work on a variety of ferritins and on transferrin–receptor interactions.

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