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Editorial

Special issue on ferritin

The advent of an oxygen-rich environment transformed Earth's atmosphere into a milieu suitable for the evolution of aerobic metabolism and complex life. Although this transformation was crucial to the development of aerobic life as we know it, living organisms had to adapt and develop strategies to deal with the evolution of an oxic environment. In early life, the abundant and water soluble ferrous iron was a stable species until oxygen appeared. The oxidation of ferrous iron by molecular oxygen led to the very insoluble ferric iron and to the production of reactive oxygen species (ROS), the bi-products of aerobic metabolism. One of the means to protect unicellular and complex multicellular organisms from the potentially toxic effects of ROS and radical chemistry is ferritin, a ubiquitous iron storage, biomineralization and detoxification protein. Ferritins belong to a family of natural, highly conserved supramolecular nanostructures designed to sequester thousands of iron atoms in the form of biologically available hydrous ferric oxide mineral core that is accessible for biologic use. They have highly conserved three-dimensional structures consisting of either twelve or twenty-four similar or identical subunits. In the case of the 24-mer protein, these subunits form a shell-like structure with internal and external diameters of 8 and 12 nm, respectively where thousands of iron atoms can be stored. Numerous studies have been directed at elucidating the mechanism of metal storage and release in ferritin and have demonstrated that the eight hydrophilic channels facilitate and direct the influx and efflux of metal ions and small molecules across the protein shell. While ferritin is mainly found in the cytoplasm of cells, other types (mitochondrial, nuclear, and secretory ferritins) have been reported.

In this special issue, recent advances and approaches addressing structural, biophysical and biochemical properties of a variety of ferritins and ferritin-like proteins are discussed. Current knowledge of the different types and roles of ferritins in cell biology, regulation of cellular iron homeostasis, oxidative damage, physiological and pathological processes is reviewed. By taking advantage of the ferritin cage for materials synthesis, new classes of materials with a wide range of application from nano-devices to biomedicine have been developed. These more recent uses of ferritin are also covered in this volume.

The first chapter is a comprehensive review by Simon C. Andrews about the evolutionary journey of the ferritin superfamily and their divergence from a primitive group of prokaryote proteins, the erythrins (Er) to more complex molecules with unique properties and physiological functions. Three distinctive types of iron storing proteins are reported: the more classical and universal 24-mer ferritins, the heme-containing 24-mer bacterioferritins of prokaryotes and the prokaryotic 12-mer Dps proteins. Robert R. Crichton et al. provide an excellent overview and detailed comparison of the structures of ferritins and related proteins in the second chapter. The paper systematically introduces the reader to the structures and interactions of the ferritin subunits leading to the formation of the protein shell.

Several other contributions (Chapters 3 through 5) focused on the mechanism of iron uptake and release in a number of ferritins. Fadi Bou-Abdallah presents a comprehensive review article on the physico-chemical aspects of the ferritins and provides a detailed mechanistic and comparative approach of the iron oxidation and hydrolysis chemistry of a number of mammalian and bacterial ferritins. In a thorough and lucid discussion of the mineralization processes of iron core formation in the ferritins of prokaryotes, Nick E. Le Brun and coworkers reviewed in depth how differences in the chemical and three-dimensional structures of the so-called ferroxidase centers of the two classes of prokaryotic ferritins, known as bacterioferritins (BFRs) and ferritins (Ftns), give rise to two different mechanisms of iron storage. Richard Watt covers the processes of iron removal from ferritin by a variety of chemical and electrochemical methods including chemical reduction, chelation and long-range electron transfer reactions. Another important section in his review article focuses on the processes of anion/cation import and export across the ferritin shell and the mechanisms of iron release by ferritin in-vivo.

Another set of excellent review articles by some of the outstanding groups in the field of ferritin biology is discussed in the second part of this special issue (Chapters 6 through 10). Suzi Torti et al. review the physiological and pathological aspects of serum ferritin, its use as a clinical tool to assess iron status and the various diseases associated with iron overload or iron deficiency. Carmen Quintana and coworkers discuss the composition and distribution of the different crystalline structures in the ferritin/hemosiderin iron-containing cores in the brain of patients suffering from two neurological diseases, progressive supranuclear palsy (PSP) and Alzheimer's Disease (AD). Paolo Arosio and coauthors describe the structural properties, expression and regulation of cytosolic and mitochondrial ferritins and their respective roles in cellular iron homeostasis and iron-induced oxidative damage. James R. Connor et al. contribute an inclusive review of our current knowledge of nuclear ferritin and its role in human development and diseases. Emilia Chiancone et al. provide a clear outline of the distinctive role of the Dps proteins in bacterial resistance to general and specific stress conditions. Her chapter outlines the distinctive features of the Dps proteins that render the protection and interaction with DNA possible as well as the preferred use of hydrogen peroxide by the protein as the physiological oxidant of iron.

Jean-Francois Briat and coauthors present an extensive review on plant ferritins and their specific features in terms of structure–function relationships, cellular localization and regulatory aspects (Chapter 11). Guanghua Zhao discusses the structure–function

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relationships of phytoferritins and their implications in human health and nutrition while Daphne Pham et al. briefly introduce insect iron metabolism and provide a detailed and thorough comparative analysis of the differences and similarities between insect and mammalian ferritins (Chapters 12 and 13).

The final part of this special issue (Chapters 14 through 18) is dedicated to the use of ferritins as biological supramolecular templates that pave the way for the development of new class of materials with a wide range of electronic and biomedical applications. This section is introduced by Trevor Douglas and coworkers whose work describes the relationship between known biological function and control mechanisms in ferritin and Dps and the use of these structures as 'designer' templates for the synthesis of unique nanostructured materials. Ichiro Yamashita and coauthors report on the synthesis of metal and semiconductor nanoparticles and the use of the resulting ferritin–nanoparticle conjugates in nano-device and carbon nanotube fabrication. N. Dennis Chasteen et al. contribute an excellent and comprehensive study on the use of analytical ultracentrifugation to prepare more uniform and size controlled nanoparticle cores using the ferritin nanocage. Daniel Strongin et al. evaluate the structure of the inorganic core of reconstituted ferritin as a function of Fe-loading and the reactivity of ferritin and ferritin-derived materials with environmentally-relevant gaseous and aqueous species. Finally, Georgia C. Papaefthymiou and coworkers discuss the Mössbauer and magnetization measurements of the initial steps of iron nucleation and biomineralization, particle growth and core-size distribution in ferritin and the possible applications of these nanosize magnetic systems in nano- and biotechnology.

Despite an extensive literature following the discovery of ferritin more than 70 years ago, the protein is still attracting high interest among researchers. I hope that this outstanding collection of review articles will help stimulate further study to better understand and clarify the many biological functions of ferritin and possibly uncover new and unexpected features of this important protein. I am extremely pleased to have many of the world's foremost scientists in the field of ferritin and cellular iron homeostasis contribute excellent review articles to this special issue. I wish to thank all the authors and reviewers whom without their invaluable work, time and effort this special issue would not have been possible.

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 then accepted an appointment as a research scientist in the Chemistry Department at the University of New Hampshire 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, 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 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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