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Structural and mechanistic insights into the iron processing by vertebrate ferritins

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Ferritins are proteins in the cell that concentrate thousands of iron(III) ions as a solid mineral.[1] The ferritin molecule is a multimeric system forming an external cage around the storage cavity. Iron(II) enters the protein shell through ion channels, and then along each subunit parallel to the cavity, reaches the active site where it is oxidized by O₂ and eventually enters the cavity.[2] In vertebrate ferritins, like the frog M ferritin here studied, this path is about 40 Å long. Data on iron-ferritin are available for bacterioferritins,[3] for the anaerobe *Pyrococcus furiosus*[4] and for the marine pennate diatoms *Pseudo-nitzschia multiseries*. [5] The latter is an eukaryotic ferritin that is largely divergent from those of other eukaryotes. Besides bacterioferritins, where iron can be cofactor and/or substrate, studying iron in ferritins is difficult because the protein provides only weak interactions to iron, which moves without resting at any tight binding site; the transient nature of protein-iron interactions translates into undetectable iron binding in the crystals. In bacterioferritins iron is well detected but its function is controversial.[3] Understanding the protein capability i) to attract and guide iron along the path, ii) to keep it at the catalytic oxidation site for the time needed for the oxidation/coupling reaction to occur, and iii) to avoid any definitive sequestration of the metal at protein binding sites is an intellectual challenge. A soaking/flash freezing method has been developed to allow aerobic and anaerobic addition of iron(II) to bullfrog[6] and human ferritin crystals. Multi-wavelength anomalous diffraction data have been exploited to unambiguously detect the iron atoms in ferritin crystals. The method has allowed us to observe for the first time the iron binding sites to a vertebrate ferritin and to see how they evolve with time. The structural data, together with stop-flow kinetic data, provide new information about the mechanism for iron processing by ferritins.

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