

## The Ferritin Fe and O Stories: Protein, genes and mRNA

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Ferritins are at the intersection of Fe and O metabolism (1). An ancient, protein family, ferritins share a unique nanocage protein structure, built of self-assembling subunits (4-helix bundles with variable amino acid sequences), that concentrates iron  $\sim 10^{14}$  fold above the solubility to match cell need. The ferritin iron concentrate, a hydrated ferric oxide mineral, forms in protein cavities, 5-8 nm in diameter. During stress the ferritin mineral is also a sink for excess iron that consumes dioxygen in the 24 subunit maxi-ferritins of animals, plants, or a sink for hydrogen peroxide that consumes iron, in the 12 subunit, bacterial-specific, mini-ferritins, also named *dps* proteins. The catalytic ferroxidase sites in maxi-ferritins, which couple ferrous and dioxygen substrates to form di-ferric mineral precursors via a diferric peroxo intermediate, are in the center of each four helix bundle. Characterization by Mössbauer, EXAFS resonance Raman and UV-vis spectroscopies, and protein engineering reveal the sites are homologous to di-iron cofactor sites in oxygenases. In mini-ferritins, the catalytic sites are relatively unexplored and appear to be at the helix-helix interfaces between subunit pairs. While protein sites that channel ferroxidase products to the cavity for mineralization remain unidentified, the site for chelation of mineralized iron after reduction, studied by crystallography, CD spectroscopy, chelation kinetics and protein engineering, is a set of eight gated pores, symmetrically arrayed around the nanocage at the junction of subunit triples, that are selectively sensitive to temperature, pH and mM urea

The biosynthesis of ferritin is regulated at two genetic steps: 1- Ferritin DNA transcription responds to cytokines and oxidants through an ARE (antioxidant response element); 2- FSSerritin mRNA translation responds to both iron and oxidants through an IRE (iron response element), part of a combinatorial family of mRNA regulators (2). ARE and IRE signal responses are synergistic. The IRE in ferritin mRNA is one of combinatorial family of related, stem-loop structures in a set of mRNAs, selectively recognized by the same repressors, but with affinities that create a graded set of responses to the same signals. Part support: NIH - DK 20251.

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2. Theil, E.C. and Eisenstein, R.S. (2000) *J. Biol. Chem.* 275:40659.