MS-INFINITE	*Pioneer MS equipment and Automated Sample Preparation unit to boost New Therapies Development*

Explanations of Ferritin Molecule

Biological species use iron in its different forms since almost the beginning of life on earth. The chemistry of iron in a water based environment containing oxygen is dominated by the iron(III) stage with the aqueous Fe3+ ions strong tendency to hydrolyze and the formation of insoluble polynuclear iron-oxide-hydroxide polymers of complex compositions [1].

In this form the availability of iron for biochemical and biological processes is much reduced or very much limited. Nevertheless, iron has a prominent role in biology. Nature has found ways for iron to be used in many different biological prominent reactions (e.g. oxygen/carbon dioxide transportation in organisms, enzymatic hydroxylation, etc.), to recover it from defunctionalized cells or molecules (glycosylated hemoglobin), to stock and retrieve it from there again, to transport it in an aqueous environment at physiological pH-values without hydrolysis and produce new biological active components (e.g. hemoglobin, cytochromes, etc.).

For this complex recycling to work, a great number of sophisticated biochemical processes use evolutionary optimized molecules that allow the efficient work of all cells [2]. The main function of ferritin which is a species and tissue specific giant, spherical protein complex is to stock iron in the interior of the protein shell in the form of crystalline, nanoparticulate, metastable ferrihydrite (approximate composition $\{[FeO(OH)]_8[FeO(H_2PO_4)]\}$ from where the iron can be mobilized again by molecular signals.

It also protects the cell compartments from free iron that can produce very reactive hydroxyl radicals ($OH^{\cdot}$, Fenton reaction, redox stress) from hydrogen peroxide. It therefore captures and buffers the iron within a cell which enables the survival of cells.

Iron enters ferritin in its Fe(II) state and is oxidized at negatively charged di-iron ferroxidase centers, localized in the H-subunits. Fe(III) then migrates to nucleation centers principally located at the inside of the L-subunits within the interior of apo-ferritin protein shell.

Mice deficient in ferritin die in the embryo stage. Ferritin is part of the cellular fluid - the cytosol - the cell nucleus compartment and of mitochondria. At the organ level the liver's stores of ferritin are the most important iron reserve in the body.

The protein in its iron free state (apoferritin) has a molecular weight of about 450 kDa which goes up to about 900 kDa when the protein is filled with up to about 4500 iron(III) in the form of ferrihydrite. The protein is built with 24 subunits of two types called L (low molecular weight with 174 amino acids (AS)) and H (high molecular weight with 182 AS) [3] in different proportions of these units. Depending on the ratio of these subunits 24 different isoferritins are possible. This ratio is said to be tissue specific. Apart from variable H/L ratio the protein can be modified by glycosylation at certain amino acid side chains (e.g. L-serin, L-threonine, L-tyrosine, L-hydoxylysine, L-hydroxyproline side-chain groups). This makes ferritin a very complex type of biomolecule that is very challenging to correctly quantify at the low levels found in serum.

Bacteria (150 AS to 160 AS), plants (about 200 AS), insects, and all higher developed creatures (approx. 170 AS to 180 AS) use a great number of different ferritin types. Ferritin is considered a cornerstone in human iron status evaluation [4],[5],[6].

Ferritin acts as a buffer against iron overload and iron deficiency in a cell. The many different functions of ferritin in an organism are still a matter of intense research and not yet fully understood.

Normal level of ferritin in blood serum differ between men, woman, children (6y to 15y), infants (1 month to 5 month) and newborns. Ranges are from 7 ng/mL up to 300 ng/mL. After breakdown of ferritin within lysosomes iron is found in the form of hemosiderin.

Literature References:

[1] Iron oxides in the laboratory, Udo Schwertmann, Rochelle M. Cornell, VCH, (1991) ISBN 3-527-26991-6. The iron oxides, Udo Schwertmann , Rochelle M.Cornell, Wiley-VCH (2003), ISBN 978-3-527-30274-3.

[2] The Ferritin-like superfamily: Evolution of the biological iron storeman from a rubrerythrin-like ancestor, Simon C. Andrews, Biochimica et Biophysica Acta (2010) 1800, 691–705.

[3] X-ray structures of ferritins and related proteins, Robert R.Crichton, Jean-Paul Declerq, Biochimica et Biophysica Acta (2010) 1800, 706–718.

[4] Iron metabolism, From molecular mechanisms to clinical consequences, Robert Crichton, Wiley Fourth ed. (2016), ISBN 978-1-118-92561-4.

[5] Iron therapy, With special emphasis on intravenous administration, Robert R.Crichton, Bo G.Daniellson, Peter Geisser, UNI-MED Verlag AG, Bremen-London-Boston, 4th Ed. (2008), ISBN 978-3-8374-1077-8.

[6] Critical review, Ferritin, cellular iron storage and regulation, Paolo Arosio, Leonardo Elia, Maura Poli, International Union of Biochemistry and Molecular Biology (2017), 69(6), 414-422.