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Commentary
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Human transferrin: An inorganic biochemistry perspective

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Introduction

Iron is essential for life and, with the rare exception of some Lactobacillus species and the bacteria Borelli burgdorferi , virtually all living organisms require this element to propagate and survive. The biological selection of iron for such a fundamental role resulted from its high abundance on the Earth's crust, its great bioavailability in the reducing primeval environment and its versatile redox chemistry, which can be finely tuned with a precise choice of ligands. However, iron was rendered poorly bioavailable by the cyanobacterial explosion and the consequent Great Oxidation Event occurring 2.4 million years ago. The accumulation of molecular oxygen in Earth's atmosphere and oceans promoted iron oxidation, hydrolysis and mineralization in most aqueous environments. Furthermore, in the presence of oxygen, the iron redox activity became a potential hazard, capable to promote the generation of reactive oxygen species (ROS) and oxidative damage to biomolecules [1].

The increase in oxygen concentration allowed the development of aerobic respiration which produces energy far more efficiently than what was previously achieved by anaerobic organisms. This led to the expansion of aerobic organisms, which eventually developed into multicellular organisms and later into vertebrates. The poor solubility of iron and its role as a pro-oxidant agent posed a difficulty for these organisms which need to transport iron between the places of absorption and storage, and cells utilizing it. In this context, the transferrin (Tf) family of proteins, consisting of high affinity iron-binders capable of ensuring the safe transport of iron in circulation, evolved as a solution probably ubiquitous to all metazoans.

Here in, we provide a review of Tf structure and biochemistry, with a focus on human serotransferrin (hTf). An overview of Tf structure, including the characterization of the high-spin d^5 Fe(III) centers by magnetic spectroscopic methods, and its role on the mechanisms of iron-binding and release is presented and the functional role of Tf post-translational modifications (PTMs) and their impact in Tf function is discussed.

Transferrin physiology

A protein of the Tf family was first identified in 1944 as an iron-binding component of egg white. Shortly after, serotransferrin was identified in the human blood plasma. Since then, the Tf family of proteins has been widely studied and its members characterized in a diversity of species.

Humans express three members of the Tf family: lactoferrin (Lf), melanotransferrin (MTf) and Tf. Lf is present in milk and other secreted fluids, such as tears, saliva, bile and respiratory pathway fluids. This protein plays an important role in the innate immune system. Lf has the ability to bind iron over a broad range of pH values, preventing its acquisition by most pathogenic bacteria. However, this evolutionary restriction of iron availability led some bacteria, such as Neisseria meningitidis, to develop the capacity to directly acquire Lf-bound iron, which involves the expression of specific Lf receptors.

MTf is an iron binding protein first identified in human skin cancer. Since, the expression of MTf has been shown in several cell types, mainly in the salivary glands, skin and kidney. MTf primarily occurs as a membrane anchored protein, although it might be secreted or shredded into the serum, and contrary to other Tf family members, it can only bind a single ferric ion. MTf is unlikely to have a significant role in regular iron metabolism, but is thought to play an important part in tumorigenesis and tumor iron metabolism.

Tf is mainly an iron carrier present in the blood plasma, the interstitial fluid, lymph and cerebrospinal fluid Tf ensures iron remains soluble under physiological aqueous conditions and prevents it from participating in redox reactions. Tf constitutes a main defense of the innate immune system, by sequestering iron from pathogenic bacteria. However, similarly to Lf, several pathogens have developed the ability to acquire Tf-bound iron through specific receptors Tf-bound iron is also one of the major signals for the regulation of hepcidin expression, the hormone which controls iron absorption and release into circulation [2].

The main location of Tf synthesis are the hepatocyte , but other significant expression sites include Sertoli cells, oligodendroglial cells, brain capillary endothelial cells, macrophages, lymphocytes and fibroblasts. Tf levels relate with body size and metabolic rate and Tf expression can also be linked to body iron stores, decreasing with iron overload and increasing in iron deficiency. The liver is thought to be responsible for the increase of Tf synthesis during iron deficiency, with Tf mRNA levels in rat and chick liver being increased due to iron nutritional restriction Tf has also been recognized as a negative acute phase protein and circulating Tf levels decrease during inflammation. However, the molecular mechanisms involved in the regulation of Tf expression are not yet fully understood. The structure of the Tf gene provides important clues and Tf synthesis seems to be mainly regulated at the transcriptional level. Tf expression is thought to be constitutively high in the hepatocytes, but regulated by an intricate network of factors in other cell types Similar to Tf expression, its catabolism correlates with body weight. 10% of Tf breakdown seems to be hepatic, but a larger amount may be released into the bile. Nevertheless, changes to blood plasma transferrin levels have been primarily attributed to a decreased expression of the protein [3].

In healthy individuals, Tf concentration in the blood plasma is approximately 2.5 g/l, presenting a typical iron saturation of 30% The protein half-life in circulation is close to 8 days, but the half-life for iron recycling is only 2 hours. This means that although Tf only bears

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a small fraction of the total body iron (~3 mg), it is responsible for the recycling and distribution of all iron necessary for hematopoiesis (~25 mg/day) [4].

Transferrin cycle

During its life time, Tf may participate in up to one hundred cycles of cellular iron delivery The Tf cycle for cellular iron uptake is a well understood process. The mechanism includes the binding of the iron-loaded Tf to transferrin receptor 1 (TfR1) at the cell surface, leading to the formation of a dimeric TfR1 adduct with two Tf molecules. The next step consists in endosomal uptake of the Tf/TfR complex through the formation of clathrin-coated pits and their internalization into the cytoplasm. Subsequently, the endosomal pH is lowered to about 5.6 by an ATP-dependent proton pump allowing loss of the clathrin coat and favoring iron release from transferrin. Iron release from Tf is further potentiated by the action of a plasma membrane ferrireductase (Steap3). In fact, the reduction of ferric iron is a requirement to allow iron transport into the cytosol, which occurs through divalent metal transporter 1 (DMT1). After iron release, the recycling of the iron-free Tf (apo-Tf) takes place. The Tf/TfR complex returns to the plasma membrane where the neutral pH environment favors apo-Tf dissociation to the extracellular fluid. The recycled apo-Tf becomes available to bind additional iron and engage in further rounds of cellular iron uptake [5].

Conclusions

An overview of the structure and function of hTf with a special focus on the bioinorganic chemistry behind this iron transporter protein and the chemical modifications that may affect its iron binding capacity is delivered herein.

We have seen nearly eight decades of research since hTf was first identified. Accordingly, there is now a good understanding of hTf fundamental role in systemic iron transport and cellular iron uptake. However, hTf biochemistry has proven to be complex and several aspects compounding the rich life of this protein remain unclear. Therefore, great interest exists to fully clarify the molecular mechanisms involving Tf in human health and disease. To date, the physiological and molecular factors regulating hTf serum levels are still poorly understood and the iron distribution between iron binding sites in vivo is still puzzling. Furthermore, key aspects of the endosomal iron release mechanism need further clarification. The requirement for an iron chelator to promote endosomal iron release has been inferred, but the identity of such molecule and how it interacts with Tf continue to be elusive. Recent X-ray crystallography structures of semi-opened hTf containing sulphate or citrate (PDB: 6JAS) at the iron binding site may shed valuable light over this subject. Similarly, the role of non-synergic anions and the identity of KISAB sites need to be ascertain.

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None

Conflict of Interest

None

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