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].

a

During its life time, Tf may participate in up to one hundred cycles of cellular iron delivery e Tf cycle for cellular iron uptake is a well understood process. e 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. e 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). A er iron release, the recycling of the iron-free Tf (apo-Tf) takes place. e Tf/TfR complex returns to the plasma membrane where the neutral pH environment favors apo-Tf dissociation to the extracellular uid. e recycled apo-Tf becomes available to bind additional iron and engage in further rounds of cellular iron uptake [5].

C

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 modi cations that may a ect its iron binding capacity is delivered herein.

We have seen nearly eight decades of research since hTf was rst identi ed. 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. erefore, 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 clari cation. e 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

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None

1. R.R. Crichton (2001) The importance of iron for biological systems R.R. Crichton John Wiley & S f تي D w 1. ٨ ٢