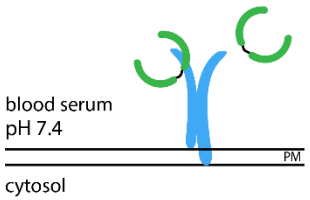
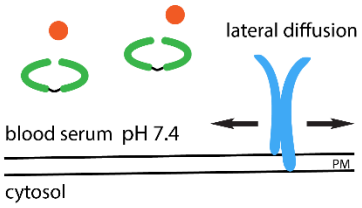
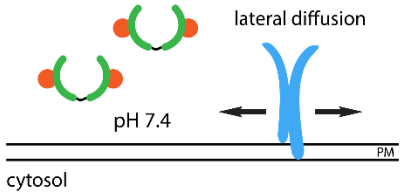
(H) Transferrin & receptor recycling, pH-mediated transferrin release



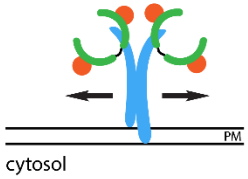

(A) Interface of blood & cell




(B) Iron-bound transferrin

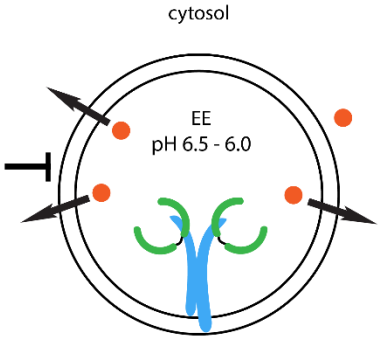



(C) Transferrin-bound receptor

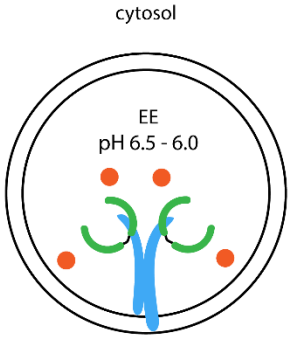



(D) Clathrin-mediated endocytosis

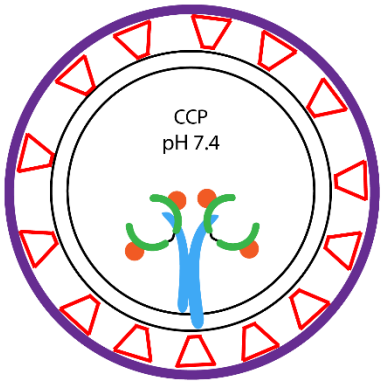

(G) pH-mediated iron release




(F) Progression to early endosome




(E) Formation of a clathrin-coated pit




(I) Disruption of endosomal pH → disruption of iron release

(J) Affinity of Tf to receptor depending on amount of bound Fe

| Tf state | pH 7.5-7.0 | pH 6.5-6.0 |
|---|---|---|
| Tf | + | +++ |
| Tf-Fe | ++ | ++ |
| Tf-Fe-Fe | +++ | + |

**Figure 1. Iron uptake into cells from the blood serum via clathrin-mediated endocytosis. (A)** Among other molecules, the blood serum contains free iron in the form of $Fe^{3+}$ (orange) and serum transferrin proteins (green). At the plasma membrane (PM) the unbound serum transferrin has very low affinity for its receptor (blue), which has a TM domain and diffuses along the PM. **(B + C)** A serum transferrin protein can bind two iron cations. The binding of iron leads to a conformational change of the serum transferrin protein, which renders the protein more stable and increases the affinity for its receptor. The two iron-bound state (holo-transferrin) has a higher receptor affinity than the single iron-bound state (mono-transferrin), which in turn has a higher affinity than the unbound transferrin (apo-transferrin). The serum transferrin receptor can bind two loaded transferrin proteins. **(D)** When a serum transferrin receptor (blue) encounters a forming clathrin-coated pit (CCP), it directly binds to the AP2 adaptor (red), which links the receptor to the clathrin coat (purple). **(E)** The receptor is engulfed together with its bound transferrins and irons into a CCP, and subsequently delivered to an early endosome (EE). **(F + G)** The pH in the EE drops to 6.5 - 6.0, which leads to a conformational change of the serum transferrin protein and to the release of the bound irons into the EE lumen. The now free iron is reduced by an endosomal ferrireductase and transported across the endosomal membrane via the zinc transporter ZIP14 or the divalent metal transporter 1 (DMT1) [2]. **(H)** The transferrin receptor is recycled to the cell surface where the change in pH results in the disassociation of the transferrins back into the blood. **(I)** A pulsed perturbation (⊣) that disrupts the endosomal pH leads to a disruption of the release of bound iron from the transferrin. The iron, the transferrin and the receptor are recycled back to the plasma membrane. The result is a reduced or absent iron uptake into the cell, despite the ongoing internalisation and recycling of transferrin. **(J)** This table shows the affinity levels of transferrin (Tf) to its receptor depending on how many irons (Fe) are bound to transferrin. This affinity changes along with the pH. At the outside of the plasma membrane, where the pH is slightly alkaline, the fully loaded transferrin has a high affinity for its receptor. This ensures that the iron-loaded transferrin is internalized together with the receptor and the iron is released into the cytoplasm. At this stage, the pH is below 6.5, which leads to a high affinity for the unloaded transferrin to its receptor, which ensures that both the receptor and the transferrin are recycled back to the PM, where the higher pH leads to the dissociation of transferrin.

References:

[1] Script *Cellular infection*, p. 17, 18.
[2] D.J.R. Lane et al. (2015). Cellular iron uptake, trafficking and metabolism: Key molecules and mechanisms and their roles in disease. Biochimica et Biophysica Acta. 1853 (5), 1130–1144.
[3] The 3D protein structures provided by the Protein Data Bank (PDB, www.rcsb.org) inspired the illustrations of serum transferrin and the serum transferrin receptor.