Determinants for iron uptake on ferritin and on the transferrin receptor.

L.C. Montemiglio[1,2], C. Testi[1,3], P. Ceci[2], E. Falvo[2], M. Pitea[1], C. Savino[2], A. Arcovito[4], G. Peruzzi[3], P. Baiocco[3], F. Mancia[5], A. Boffi[1,3], A. des Georges[6], B. Vallone[1,2,].

[1]Dept of Biochemical Sciences Sapienza University of Rome, Italy, [2]CNR-IBPM, Rome, Italy
[3]CNLS@Sapienza, IIT, Rome, Italy, [4]Università Cattolica del Sacro Cuore, Rome, Italy, [5]Columbia University Medical Center, New York, USA, [6]ASRC-CUNY, New York, USA
beatrice.vallone@uniroma1.it

Human transferrin receptor-1 (CD71) guarantees iron supply by endocytosis upon binding of iron-loaded transferrin and ferritin to CD71. Viruses and the malaria parasite exploit CD71 for cell invasion and epitopes on CD71 for interaction with transferrin and pathogenic hosts were recently identified. We provide the molecular basis of the human ferritin-CD71 interaction by the 3.9 Å resolution single-particle cryo-electron microscopy structure of their complex and by validating our structural findings in cellular context [1]. The structure of the H-Ft/CD71 complex revealed the specific sites on CD71 to be hooked by ferritin for physiological access to cell through the CD71 "iron door". Moreover, it accounts for a Tf-independent binding of ferritin to the receptor, allowing differential regulation of iron uptake, and indicates a physiological role for the CD71 apical domain, unassigned to date. The contacts between the heavy-chain ferritin and CD71 largely overlap with arenaviruses and Plasmodium vivax binding regions in the apical part of the receptor ectodomain [2,3]. Our data account for transferrin-independent binding of ferritin to CD71 and suggest that select pathogens may have adapted to enter cells by mimicking the ferritin access gate and it provides a sound structural basis to elaborate on the possibility of developing alternative ferritin-like anti-viral or anti-parasite therapeutic ligand, be it an antibody or a peptidomimetic capable of blocking the "common contacts" epitope on CD71 residue, and to further engineering ferritins as nanocarriers and theranostic agents.

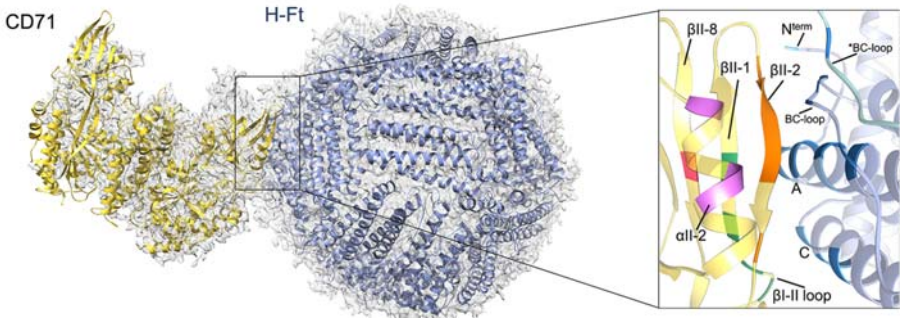

Figure 1: The complex between human ferritin and the CD71 receptor and details of contact interactions.

References

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