Single Particle Cryo-EM structure of human Ferritin and Transferrin Receptor complex

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Cryo electron microscopy (cryo-EM) is becoming a very promising biophysical technique in nanotechnology, thanks to the recent introduction of direct electron detectors and the improvement of computational tools for image processing. In cryo-EM, just a few microliters of homogeneous solution containing the nanoparticles of interest are sufficient to reconstruct its structure, up to the atomic resolution. The availability of automated data collection systems and single-particle image processing software make this task achievable within few weeks of work.

In this context, we present the cryo-EM structure of the complex formed between the human Ferritin (Ft) and human Transferrin Receptor 1 (hTfR1). Ferritin is a globular protein whose primary role is to store iron within the cells; its 24 subunits self-assemble spontaneously in a hollow cage-like spherical structure. This peculiar nano-sized quaternary structure makes it an excellent nano-carrier for drugs and diagnostic agents with diverse applications in nanomedicine for the development of theranostic nanoparticles. More importantly, Ferritin can enter cells through hTfR1, a receptor hugely over-expressed in most types of tumors. This natural feature of Ferritin allows its exploitation as potential nano-vector for targeted delivery of anti-cancer drugs to malignant cells. However, structural information related to the Ft-hTfR1 interaction was to date still missing.

We obtained the structure of Ft-hTfR1 complex at 4.2 Å resolution by single-particle cryo-electron microscopy, revealing for the first time the structural basis of this interaction. We observed that few short motifs upon the H-Ferritin homopolymer recognize a precise epitope on hTfR1.

The current structural data provide important information to understand the physiological role of Ft-hTfR1 system and pave the way to a better use of Ferritin as a nanotechnological tool for cell targeted delivery.