MS07-P22 | Structural Comparison Of Two Mammalian Multicopper Oxidases, Hephaestin And Ceruloplasmin

Zaitsev, Viatcheslav (Independent researcher, Dundee, GBR); Lindley, Peter (ITQB NOVA, Oeiras)

The evolutionary family of multicopper oxidases (MCO) includes laccase, ascorbate oxidase, CueO, Fet3p and ceruloplasmin [1-2]. A new mammalian MCO and ceruloplasmin (Cp) evolutionary paralogue, hephaestin (Heph) has been recently discovered [3-5]. While Heph shares ~50% sequence identity with serum Cp, it includes an additional transmembrane domain at the C-terminus and a short cytoplasmic tail.

A structural model for the ecto-domain of human Heph has been created using Phyre2 [6] and Swiss-Model [7] protein modelling software. The Heph model shows high similarity to the human Cp (hCp) structure [8] with the overal RMSD value of 0.45 Å. Detailed structural comparison of six integral copper centres and putative divalent cation binding sites has revealed that Heph, in contrast to hCp, contains the 3rd 'blue' mononuclear copper site in domain 2. In addition, three putative iron binding sites in domains 2, 4 and 6 were identified in the Heph structure, whereas hCp holds only two iron binding sites in domains 4 and 6 [1,8]. Based on these observations, distinct physiological roles of the two ferroxidases, intracellular Heph and plasma blood hCp, will be discussed.

[1] https://slavazaitsev914078364.wordpress.com
[2] P.Lindley et. al. (1999). In: Perspect. Bioinorg. Chem., 4: 51-82
[3] C.Vulpe et. al. (1999). Nat. Genet. 21: 195–199
[4] B.Syed et. al. (2002). Protein Eng. 15: 205-214
[5] H.Chen et al. (2010) J. Nutr. 140: 1728–1735.
[6] L.Kelley et. al. (2015). Nature Protocols 10: 845-858
[7] A.Waterhouse et. al. (2018). Nucleic Acids Res. 46(W1): W296-W303
[8] I.Bento et. al. (2007). Acta Cryst. D63(2): 24O-248