MS12-P09 | STRUCTURAL COMPARISON AND EVOLUTIONARY RELATIONSHIPS BETWEEN CERULOPLASMIN, HEPHAESTIN AND BLOOD COAGULATION FACTOR VIII

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Copper proteins form an extremely diverse group of proteins with a broad variation in function ranging from electron transfer, metal transport, oxidation of a variety of substrates, to the blood coagulation factors V and VIII (FVIII). A separate class of multicopper oxidases (MCOs) includes laccase, ascorbate oxidase, metallo-oxidases CueO and Fet3p, hephaestin and ceruloplasmin [1-3]. It is widely accepted that the MCOs have evolved from a two-domain ancestral protein (gene duplication of cupredoxin).

The A domains of FVIII show some 40% sequence identity to the six-domain ceruloplasmin. Unlike ceruloplasmin, FVIII contains a large insertion domain B and two extra domains C1 and C2 at the C-terminus. Structural comparisons of human ceruloplasmin (hCp) [2] and its evolutionary paralogue, hephaestin (Heph) [3], with the three X-ray structures of recombinant FVIII [4-6] have been undertaken. The A domains of FVIII heterotrimers show significant similarity to the hCp/Heph structure with the overal RMSDs varying from 1.4 to 1.7 Å. However,a detailed comparison of the copper binding sites indicates that FVIII may have evolved from the Heph precursor, but not from that of hCp, whilst losing the interdomain trinuclear copper cluster and the mononuclear copper of domain 4. The evolutionary relationships within the broader copper proteins superfamily will be discussed.

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