MS08-P04 | Structural Basis Of Ascorbate-Dependent Iron Reduction By Human Dcytb Involved In Intestinal Iron Absorption

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Duodenal cytochrome *b* (Dcytb) is a Fe^{3+} reductase that was identified in the duodenal brush border. Since DMT-1 favors the absorption of divalent metal including Fe^{2+}, the reduction of Fe^{3+} to Fe^{2+} by Dcytb in the duodenum is essential for effective intestinal iron absorption. Dcytb is an integral membrane protein that catalyzes reduction of nonheme Fe^{3+} by electron transfer from ascorbate across the membrane. Here we report the crystallographic structures of human Dcytb and its complex with ascorbate and Zn^{2+} [1]. Each monomer of the homodimeric protein possesses six transmembrane helices and cytoplasmic and apical heme groups, as well as cytoplasmic and apical ascorbate-binding sites located adjacent to each heme. Zn^{2+} coordinates to two hydroxyl groups of the apical ascorbate and to a histidine residue. Biochemical analysis indicates that Fe^{3+} competes with Zn^{2+} for this binding site. These results provide a structural basis for the mechanism by which Fe^{3+} uptake is promoted by reducing agents and should facilitate structure-based development of improved agents for absorption of iron.

[1] Ganasen et al. *Commun. Biol.*1,120 (2018)