第 524 回 難研セミナー
第 97 回 難治疾患共同研究拠点セミナー

下記により難研セミナーを開催しますので、多数御来聴下さい。

記

日　時： 2014 年　10 月　28 日（火）17:00～18:00

場　所： M&D タワー　22 階　共用セミナー室 4

演　者： **米谷 隆 教授**　（University of Pennsylvania）

演　題： How does hemoglobin regulate its oxygen-affinity and cooperativity?

要　旨： Human hemoglobin (Hb) is an efficient O_2-transporter in the blood. This red tetramer hemoproteins binds four O_2/tetramer at an arterial O_2-pressure of 100 torr and releases them at a venous O_2-pressure of ~40 torr (in the capillary) at 37°C, in order to deliver O_2 to the tissues, by reversibly changing its O_2-affinity depending on the O_2-pressure of the environment (the coopertivity). The current widely-accepted hypothesis of the mechanism of the cooperativity of Hb was proposed by Perutz [1], that was based upon the stereochemical molecular structures of deoxy- and oxy-Hb, which he had determined by X-ray crystallography. Deoxy-Hb has a more rigid tetramer structure (the T-quaternary structure), which constrains the coordination structure of the heme group, leading a low O_2-affinity. As four O_2 bind successively to Hb, its structure changes to a less rigid R-quaternary state, in which all the structural constraints are removed, resulted in the unconstrained coordination structure of the heme groups with a high O_2-affinity.

However, we found that the O_2-affinity of either deoxy- or oxy-Hb can be reduced as much as $>10^3$-folds by heterotropic effectors such as 2,3-BPG, IHP, and BZF without detectable changes in the T-/R-quaternary/tertiary structure as well as the coordination structures of the heme group [2-4]. Thus, we were not able to find the casual correlation between T-/R-quaternary structures and the low- and high O_2-affinity, as proposed by Perutz [1].

In Hb, the apparent O_2-affinity is controlled by regulating the physical barrier of globin against the migration of O_2 through protein matrix from the “caged” state to solvent [5-7]. The physical barrier is lowered by the heterotropic effector-linked, high-frequency thermal fluctuations [8], which make the protein barrier more and more transparent to small ligands like O_2. Thus, the apparent O_2-affinity of Hb is controlled by protein dynamics rather than the static T-/R-quaternary/tertiary structural changes of Hb [4].

References: [1] Perutz, M.F., *Nature* *228* (1970) 726; [2] Yonetani, T. *et al., JBC* *277* (2002) 34508; [3] Yonetani, T. & Laberge, M., *BBA* *1784* (2008) 1146; [4] Yonetani, T. & Kanaori, K., *BBA* *1834* (2013) 1837; [5] Iizuka, T. *et al., BBA* *351* (1974) 182; [6] Iizuka, T. *et al., BBA* *371* (1974) 126; [7] Yonetani, T. *et al., JBC* *249* (1974) 2168; [8] Laberge, M. & Yonetani, T., *Biophys. J.* *94* (2008) 2737.

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共催：生命情報学分野