Structural Basis of Multi-functional lipocalin-type Prostaglandin D_2 Synthase

Masashi Miyano[1], Hideo Ago[1#], Kosuke Aritake[2#], Daisuke Irikura[2#], Takashi Kumasaka[1#], Tsuyoshi Inoue[3], Masaki Yamamoto[1], Yoshihiro Urade[2], Osamu Hayaishi[2], [1]*RIKEN Harima Institute at SPring-8, Hyogo 679-5148, Japan.* [2]*Osaka Bioscience Institute, Osaka, 565-0874, Japan.* [3]*Department of Engineering, Osaka University, Osaka 565-0871, Japan.* [#]*Equally contributed authors*. E-mail: miyano@spring8.or.jp

Prostaglandin (PG) D_2 is a natural somnogen inducing non-rapid eye moving (NREM) sleep and an immuno-modulator. PGD synthase (PGDS) is responsible for the production of PGD_2. We determined the crystal structures of lipocalin-type PGDS (L-PGDS) as the first enzymatic lipocalin by using SeMet-MAD phasing at 2.1 Å resolution [1]. L-PGDS has a catalytic architecture similar to the phylogenetically independent PGDS, hematopoietic PGDS, which belongs to a sigma class glutathione S-transferase [2]. L-PGDS is a multi-functional protein which also acts as a hydrophobic ligand-binding protein. The structures with different conformations in two crystal forms suggest the structural basis of the multi-functionalities as well as the mode of the catalytic action [3]. These proposed mechanisms were consistent with the extended site-directed mutagenesis. We present the structural and functional basis of L-PGDS as a multi-functional protein relevant to the biological actions including NREM sleep promotion in the prostanoid cascade [4].

[1] Irikura D., Kumasaka T., Yamamoto M., Ago H., Miyano M., Kubata K.B., Sakai H., Hayaishi O., Urade Y., *J. Biochem. (Tokyo),* 2003, **133**, 29-32. [2] Kanaoka Y., Ago H., Inagaki E., Nanayama T., Miyano M., Kikuno R., Fujii Y., Eguchi N., Toh H., Urade Y., Hayaishi O., *Cell*, 1997, **90**, 1085–1095. [3] Kumasaka T., Irikura D., Aritake K., Ago H. et al., submitted. [4] Hayaishi O., Urade Y., *Neuroscientist*, 2002, **8**, 12–15.

Keywords: prostaglandin D synthase, lipocalin, protein crystallography