Crystal Structure of Hematopoietic Prostaglandin D Synthase Complexed of HQL-79

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Hematopoietic prostaglandin(PG) D synthase(H-PGDS) is responsible for production of PGD_2 as an allergic or inflammatory mediator in mast cells and Th2 cells[1].

We solved the crystal structure of human H-PGDS bound to the cofactor glutathione(GSH) and HQL-79, a novel inhibitor of H-PGDS in the presence of Ca^{2+} or Mg^{2+}, showing the HQL-79 molecule penetrated into the active site between Trp104 and GSH binding site with its biphenyl rings locating at the bottom of the active site, inducing the conformational change of Trp104 with a 60 degree rotation and a 3.7 A movement of the indole ring.

The surface plasmon resonance analysis revealed that the binding affinity (KD) of HQL-79 is accelerated 10-fold in the presence of both Mg^{2+} and GSH, revealing that the GSH molecule strongly bound in the Mg^{2+}-bound form helped the insertion of the HQL-79 molecule, reducing the *Ki* value to be 5 μM with 10-fold in the presence of Mg^{2+}. HQL-79 specifically inhibits H-PGDS activities competitive to the substrate PGH_2, and non-competitive to the cofactor GSH[2].

[1] Urade Y., Hayaishi. O., *Vitam Horm*, 2000, **58**, 89-120. [2] Aritake K., et.al., *submitted*.

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