Structural Basis for Prostacyclin Biosynthesis

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Prostacyclin synthase (PGIS) converts prostaglandin H_2 to prostacyclin, which is a highly potent vasodilator and inhibits platelet aggregation. This enzyme is located to the endoplasmic reticulum membrane and was assigned to the P450 superfamily as CYP8A1 when its cDNA sequence was determined. Unlike other microsomal P450s that catalyze mono-oxygenation or hydroxylation reaction, PGIS catalyzes an isomerizaton and does not need molecular oxygen, reductase or any other external electron donor. Various genome projects have identified PGIS-like sequence in the animals as low as amphibians and fish (http://drnelson.utmem.edu/CytochromeP450.html), suggesting that PGIS emerged early in vertebrate evolution. Using the recombinant human PGIS obtained from a prokaryotic expression system, we had previously determined the crystal structure of this atypical and yet physiologically important P450 in its ligand-free state. However, critical questions regarding the regioselectivity of PGIS-catalyzed isomerization and the catalytic roles of active residues remain to be answered. To this end, we have now determined the crystal structures of the ligand-free and substrate analog-bound zebrafish PGIS. The structural basis for the regioselectivity and how the enzyme may facilitate the isomerization reaction were recognized. In addition, the substrate entrance and product exit channels of PGIS were identified. Detail structural analysis and functional significance of the ligand-bound zPGIS will be presented and discussed.