Crystal structure of leukotriene C_4 synthase responsible for the cysteinyl leukotriene biosynthesis

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Leukotriene C_4 synthase (LTC_4S), which is a membrane integrated protein existing in nuclear membrane, catalyzes the conjugation between leukotriene (LT) A_4 and glutathione (GSH) to form LTC_4. LTC_4 and its metabolites LTD_4 and LTE_4 are components of SRS-A (slow reacting substance of anaphylaxis), and they are called cysteinyl leukotrienes because they have a cysteine moiety commonly. Cysteinyl leukotrienes are lipid mediators involved in smooth muscle constriction and inflammation, particularly in asthma [1]. LTC_4S is the membrane protein responsible for the biosynthesis of cysteinyl leukotrienes and a potential target for drug discovery.

The crystal structure of human LTC_4S was determined at 3.3Å resolution using the recombinant LTC_4S [2]. We established the over-expression system using *Schizosaccharomyces pombe*, and we used the expression system for the preparation of the selenomethionine derivative of LTC_4S with a Leu121Met mutation for the MAD phase calculation as well as the native LTC_4S with a histidine tag. In the crystal structure LTC_4S forms trimer structure, and there is a V-shape substrate binding cleft between two adjacent monomers. GSH, which is one of the substrates and was co-crystallized with LTC_4S, bound at the upper space of the V-shape cleft. The rest space of the V-shape cleft fits aliphatic chain of LTA_4 having two *cis*-double bonds in shape and depth, and was concluded to be the LTA_4 binding site. It would be the reason why LTC_4S discriminates LTA_4 as the other substrate specifically from xenobiotics in contrast to other GSH transfer enzymes with broad substrate specificity. Based on the crystal structure, we proposed the acid-base catalytic mechanism, and Arg31 from a monomer and Arg104 from the other monomer exert the acid and base, respectively. The crystal structure of human membrane integrated protein LTC_4S revealed the details of molecular function of the important enzyme both in the basic life science and in the practical drug discovery.

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[2] Ago, H., Kanaoka, Y., Irikura, D., Lam, B. K., Shimamura, T., Austen, K. F., and Miyano, M., Crystal structure of a human membrane protein involved in cysteinyl leukotrienen biosynthesis. (2007) *Nature* **448**, 609-612.