Crystal structure of leukotriene C\textsubscript{4} synthase responsible for the cysteinyl leukotriene biosynthesis

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Leukotriene C\textsubscript{4} synthase (LTC\textsubscript{4}S), which is a membrane integrated protein existing in nuclear membrane, catalyzes the conjugation between leukotriene (LT) A\textsubscript{4} and glutathione (GSH) to form LTC\textsubscript{4}. LTC\textsubscript{4} and its metabolites LTD\textsubscript{4} and LTE\textsubscript{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\textsubscript{4}S is the membrane protein responsible for the biosynthesis of cysteinyl leukotrienes and a potential target for drug discovery.

The crystal structure of human LTC\textsubscript{4}S was determined at 3.3Å resolution using the recombinant LTC\textsubscript{4}S [2]. We established the over-expression system using \textit{Schizosaccharomyces pombe}, and we used the expression system for the preparation of the selenomethionine derivative of LTC\textsubscript{4}S with a Leu121Met mutation for the MAD phase calculation as well as the native LTC\textsubscript{4}S with a histidine tag. In the crystal structure LTC\textsubscript{4}S 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\textsubscript{4}S, bound at the upper space of the V-shape cleft. The rest space of the V-shape cleft fits aliphatic chain of LTA\textsubscript{4} having two \textit{cis}-double bonds in shape and depth, and was concluded to be the LTA\textsubscript{4} binding site. It would be the reason why LTC\textsubscript{4}S discriminates LTA\textsubscript{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\textsubscript{4}S revealed the details of molecular function of the important enzyme both in the basic life science and in the practical drug discovery.
