3D structure and mechanism of membrane protein MGST2 identified, paving way for drug developments

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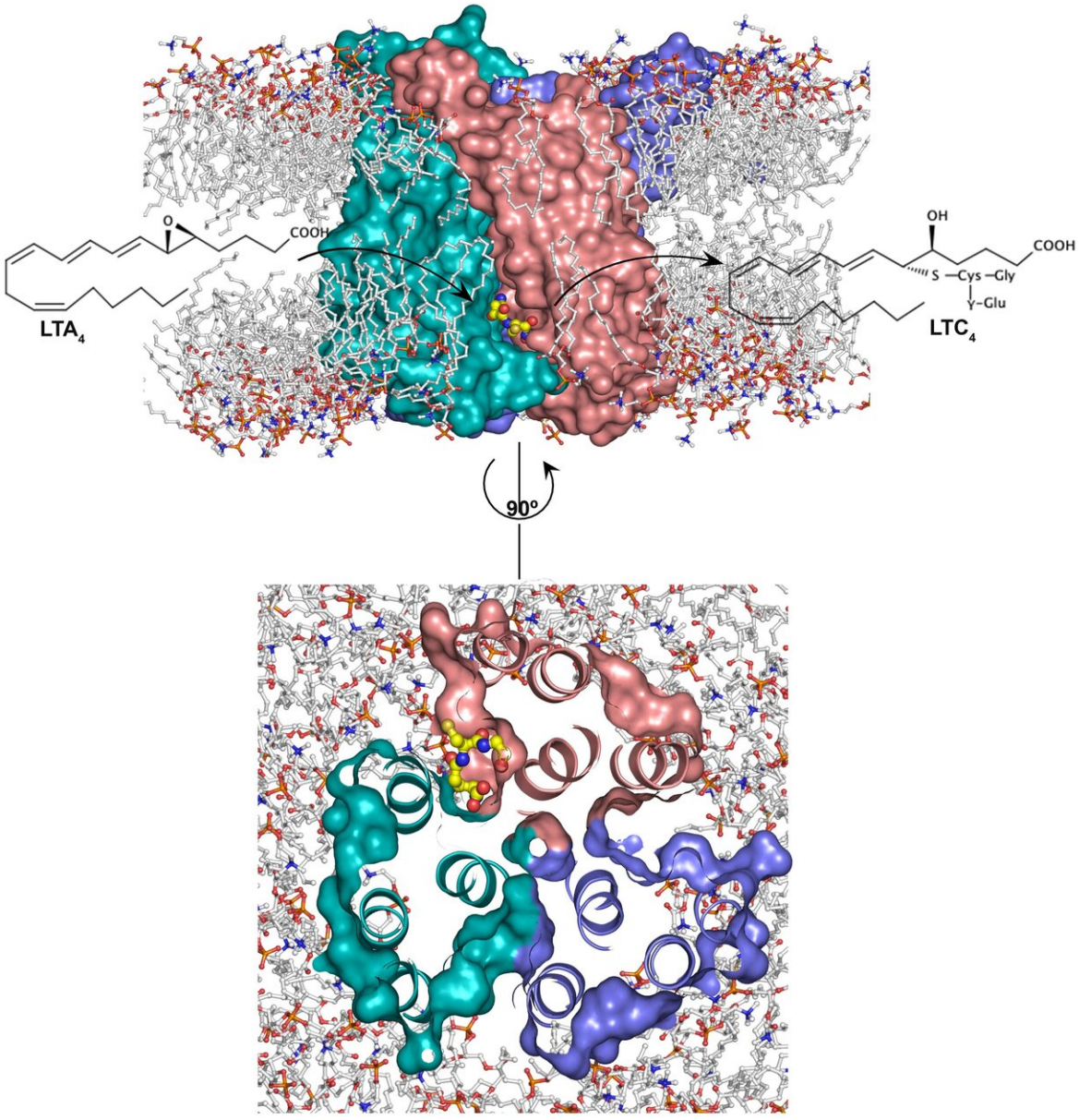

The enzyme MGST2 embedded in nuclear membranes. Image: Madhuranayaki Thulasingam

Most drugs operate via the membranes that surround the body's cells. A study by researchers at Karolinska Institutet in Sweden has now mapped the structure and mechanism of MGST2, a membrane enzyme that, amongst other things, plays a part in chronic inflammation and cancer. The study, which is published in the journal *Nature Communications*, can make a significant contribution to the development of future drugs.

All our cells are enclosed in a fat-rich membrane. The cells' equivalent to organs, the organelles, are also enclosed by membranes. Embedded in the cell's internal and external membranes are proteins that regulate a large number of vital functions. Almost half of all drugs are effective via membrane proteins, such as enzymes, receptors and transporters.

Researchers at Karolinska Institutet have now, with the aid of X-ray crystallography, molecular dynamics simulations and biochemical techniques, been able to determine the 3D structure and mechanism of an important enzyme embedded in the cell's nuclear membrane.

Three active units take turns

The membrane enzyme MGST2 (Microsomal Glutathione S-Transferase 2) is the motor of a biochemical process that causes oxidative stress and the formation of oxygen radicals and, subsequently, DNA damage and cell death.

"Membrane proteins are hard to study and it's fantastic that we've

managed to determine the crystal structure for MGST2 at high resolution," says the study's first author Madhuranayaki Thulasingam, researcher at the Department of Medical Biochemistry and Biophysics, Karolinska Institutet. "One of the study's findings is that MGST2 is made up of three functional units that are controlled in an unusually sophisticated manner. The three units are involved in mutually coordinated movements, taking turns to perform the enzyme's function one active unit at a time."

MGST2 belongs to a larger family of enzymes that control the formation of prostaglandins and leukotrienes, signal molecules that regulate fever, pain and inflammation of the airways, joints, heart and blood vessels.

Important group for drug development

The results provide valuable information on the molecular regulation of other members of the enzyme family, many of which are important targets for future drug development.

"We hope that our results will be able to contribute to the development of drugs for many diseases characterized by increased synthesis of oxygen radicals and cell death, such as chronic inflammation, cancer and side-effects of radio- and chemotherapy," says principal investigator Jesper Z. Haeggström, professor at the Department of Medical Biochemistry and Biophysics, Karolinska Institutet.

More information: Madhuranayaki Thulasingam, et al. Crystal structures of human MGST2 reveal synchronized conformational changes regulating catalysis, *Nature Communications*, online 19 March 2021, DOI: 10.1038/s41467-021-21924-8

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