

Crystal structure enables tailoring of pharmaceuticals against asthma

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Researchers at Karolinska Institutet in Sweden have managed to elucidate the crystal structure of a human membrane protein – LTC₄ synthase – which has a major influence on the development of asthma. LTC₄ synthase is extremely difficult to analyze, and previously only low resolution information has been available on two membrane protein structures from human. The scientists now believe that their work will enable the development of new and better therapeutics against inflammations in the pulmonary tract.

Asthma attacks are caused by an acute inflammatory reaction in the airways, a reaction that is largely due to actions of LTC₄ synthase. For this reason asthma medicines often aim at blocking the downstream effects of LTC₄ synthase. However, there is a need for new pharmaceutical alternatives, since not all patients respond to the existing medicines.

Scientists at the Department of Medical Biochemistry and Biophysics have now, with the help of the two EU networks “EICOSANOX” and “E-Mep”, elucidated the three dimensional structure of the LTC₄ synthase at 2.0 Å resolution (1 Å = 1 Ångström = 10⁻¹⁰ m = 0,000 000 000 1 m). It is clear from the structure that the protein has three identical subunits, each of them consisting of four spiral structures that span the nuclear membrane. Also the exact position and characteristics of the active sites, where activating or blocking molecules can bind, have been identified. With this knowledge it is now possible to tailor new molecules that can block the LTC₄ synthase.

The new results are also very important as they can lead the way for the development of new and more effective therapeutics against other diseases. Some 40 % of the proteins of interest for pharmaceutical developments are membrane proteins. Until now detailed structural information on these proteins has been absent, and therefore it has been difficult to fully understand their function. The present study is likely to lead the way for the determination of structures of other human membrane proteins. The elucidation of more membrane protein structures will help us understand fundamental processes that take place in the cell membranes.

Facts: Proteins consist of a chain of amino acids. The length of this chain can range from a few to thousands of amino acids. The chain is then folded in a characteristic way and the 3-D structure can bind different molecules. Determining a protein structure and its biochemical characteristics helps us understand its function, and to design blocking or activating molecules which can serve as medicines. A known protein structure therefore makes it easier and faster to develop new pharmaceuticals.

Source: Karolinska Institutet

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