Structure of the molecular machine that links carbohydrate and lipid metabolism

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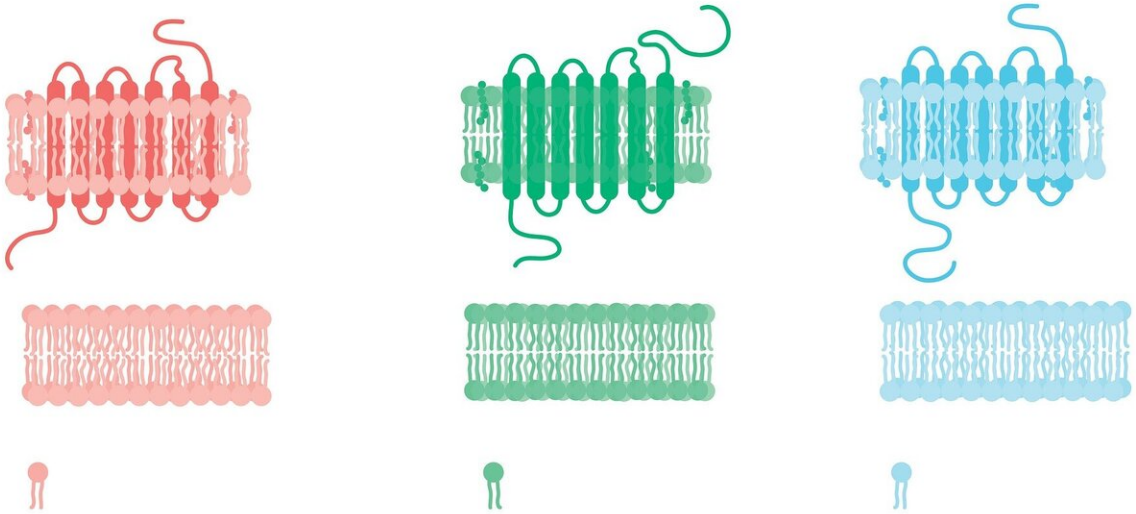

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A research team led by Dr. Kenneth Verstraete in the Unit for Structural Biology at the VIB-UGent Center for Inflammation Research has unraveled the three-dimensional structure and molecular mechanism of ATP citrate lyase (ACLY). This is a central metabolic enzyme, a protein that accelerates chemical reactions, important for the production of fatty acids and cholesterol in the human liver. The reported findings could help in targeting ACLY in cancer and metabolic diseases such as

atherosclerosis. The structure of ACLY also unmasked a crucial evolutionary relationship that radically changes our understanding of the origins of cellular respiration.

Organisms across all kingdoms of life crucially rely on a molecule called acetyl-CoA that fuels essential biochemical processes in cells, such as the production of fatty acids and cholesterol. However, acetyl-CoA is not always easily available. To produce it, the enzyme ATP citrate lyase (ACLY) needs to set in motion a sequence of chemical reactions involving other molecules such as citrate and coenzyme A. This makes ACLY a critical component for the cellular manufacturing of fatty acids and cholesterol, which have become notorious in our perception of human diet, and yet are essential molecules for life and cell integrity. However, despite decades of research on the ACLY-driven biosynthetic cycle and its importance in many facets of physiology and disease, the three-dimensional structure of ACLY and its role as a biosynthetic factory had remained very poorly understood.

The news study, conducted by the research group coordinated by Prof. Savvas Savvides (VIB-UGent Center for Inflammation Research), has made great strides in the understanding of ACLY and the reactions it regulates. Learning more about ACLY has been very challenging due to the size and modular nature of this enzyme. By employing a comprehensive structural approach that benefited from fruitful collaborations with teams from the EMBL (Hamburg, Germany) and ISB-CNRS (Grenoble, France), the VIB researchers were able to determine high-resolution structures of ACLY enzymes across different domains of life, including humans. Such international collaborations continue to prove crucial for groundbreaking research. In the words of Prof. Savvas Savvides: "This work is the result of great collaborative efforts in the spirit of integrative structural biology and has relied on state-of-the-art approaches and generous access to European synchrotron radiation facilities for structural studies."

The reported structural snapshots showed that ACLY can adopt distinct structural states as part of the multistep reaction mechanism leading to the formation of acetyl-CoA. In addition, the researchers made new evolutionary discoveries about citrate synthase, the first enzyme of the oxidative Krebs cycle. This cycle is responsible for the production of energy units in cells and is one of the most fundamental biochemical pathways on earth. The team found that citrate synthase evolved from an ancestral citryl-CoA lyase module that operates in the reverse Krebs cycle found in a wide range of bacteria. This molecular transition—from citryl-CoA lyase to citrate synthase—marked a key step in the evolution of metabolism on earth and indicates that the reverse Krebs cycle predates the oxidative Krebs cycle. This is a major evolutionary insight that had eluded scientists for decades.

Dr. Kenneth Verstraete explains: "Our tour-de-force structural exploration of the mechanism and evolution of ACLY as a central metabolic enzyme is poised to reshape our understanding of biochemistry and will facilitate efforts to target human ACLY in widespread metabolic diseases and cancer."

The central role of ACLY in human metabolism inspired its possible therapeutic relevance. For instance, to support tumor growth many cancer cells show an increase in fatty acid production which depends on ACLY. In fact, in breast and lung cancer, one observes an increased activity of ACLY. Furthermore, ACLY in the liver is a therapeutic target in metabolic disorders marked by high levels of blood triglycerides and cholesterol. Currently, the most advanced ACLY-targeting medicinal substance is bempedoic acid, which is under clinical evaluation as a promising treatment to lower low-density lipoprotein cholesterol (LDL cholesterol, the 'unhealthy' type) associated with atherosclerosis. Dr. Verstraete and his colleagues anticipate that the detailed structural and functional insights they have contributed will facilitate therapeutic targeting of human ACLY in metabolic diseases

and cancer.

The study is published in *Nature*.

More information: Structure of ATP citrate lyase and the origin of citrate synthase in the Krebs cycle. *Nature*. DOI: 10.1038/s41586-019-1095-5 , www.nature.com/articles/s41586-019-1095-5

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