Atomic structure of the mammalian 'fatty acid factory' determined

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Mammalian fatty acid synthase is one of the most complex molecular synthetic machines in human cells. It is also a promising target for the development of anti-cancer and anti-obesity drugs and the treatment of metabolic disorders. Now researchers at ETH Zurich have determined the atomic structure of a mammalian fatty acid synthase. Their results have just been published in *Science* magazine.

Synthesis of fatty acids is a central cellular process that has been studied for many decades. Fatty acids are used in the cell as energy storage compounds, messenger molecules and building blocks for the cellular envelope. Until now, individual steps of this process have been investigated using isolated bacterial enzymes. However, in higher organisms – except plants – fatty acid synthesis is catalyzed by large multifunctional proteins where many individual enzymes are brought together to form a "molecular assembly line".

As described in this week's issue of "*Science*" magazine, researchers at ETH Zurich, supported by the National Centre of Excellence in Research (NCCR) in Structural Biology at the Swiss National Science Foundation, determined the high-resolution structure of a mammalian fatty acid synthase using data collected at the Swiss Light Source (SLS) of the Paul Scherrer Institute (PSI) in Switzerland. These results crown the efforts begun in 2001 to determine the detailed structures of fatty acid synthases in higher organisms by a relatively small group of scientists at ETH Zurich. The group, consisting of Timm Maier, Marc Leibundgut and Simon Jenni in the laboratory of Prof. Nenad Ban,

published their first papers describing architectures of fungal and mammalian fatty acid synthases two years ago.

That was followed last year by two papers on the atomic structures of fungal fatty acid synthases and the mechanism of substrate shuttling and delivery in these multi-enzymes. Now this latest publication describes the atomic structure of the mammalian fatty acid synthase. These results reveal the details of all catalytic active sites responsible for iterative fatty acid synthesis and show how the flexibility of this large multi-enzyme is used for transferring substrates from one enzymatic active site to the next. The structure can be considered a milestone for future research in the field.

In addition to the fundamental scientific interest in the function of this multi-enzyme that plays a central role in primary metabolism, mammalian fatty acid synthase is also considered a promising drug target. Although most fat accumulated in animals and humans is delivered to cells by ingestion and not by de novo synthesis, compounds that inhibit the function of the mammalian fatty acid synthase induce weight reduction in animals, showing potential for the treatment of obesity and obesity-related diseases, such as diabetes and coronary disorders. Furthermore, due to the increased requirement for fatty acid synthesis in cancer cells, inhibitors of this enzyme have anti-tumor activity, making fatty acid synthase an attractive drug target for anti-cancer therapy.

Mammalian fatty acid synthase belongs to a large family of multi-enzymes, some of which are responsible for the synthesis of complex natural products with antibiotic, anti-cancer, anti-fungal and immunosuppressive properties that are of outstanding medical relevance. The structure of mammalian fatty acid synthase reveals how different catalytic domains are excised or inserted in various members of this family to yield multi-enzymes capable of synthesizing a large variety of

chemical products. The structure will facilitate the design of molecular assembly lines for the production of improved compounds. In particular, the engineering of novel multi-enzymes for the production of modified antibiotics is important in the fight against resistant strains of bacteria.

Source: ETH Zurich