

Researchers discover first protein that regulates fatty acid synthase

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Credit: Max Planck Society

Tuberculosis still represents the infectious disease with the highest fatality numbers. It is caused by mycobacteria, which mainly attack the lungs but can also affect almost any other organ. The fatty acid biosynthetic factory is an important target in the fight against this infectious bacterium. The fatty acid synthase (FAS) is considered one of

the most complex cellular machines. The team led by Holger Stark and Ashwin Chari of the Max Planck Institute for Biophysical Chemistry has now discovered a protein that commands and controls FAS function. This finding not only opens up new therapeutic venues, particularly against tuberculosis. In biotechnological applications this new control unit enables the generation of tailor-made fatty acid synthases and specialized products that could only be synthesized from crude oil. This opens the prospects in 'green biotechnology'.

Fatty [acid](#) factories are indispensable for living organisms—as are the fatty acids they produce, which are often frowned upon as fatteners. Fatty acids serve as energy stores, building blocks for biological membranes, or cellular messenger substances. In yeast and higher organisms, FAS forms a higher order structure of several enzymes. In bacteria, isolated enzymes perform the same tasks. Although FAS architecture is considerably divergent in different organisms, the enzymes involved in fatty acid production are structurally very similar.

This is especially true for FAS enzymes from yeast, fungi and tuberculosis infectious mycobacteria. Therefore, findings on yeast FAS can be directly transferred to the bacterial fatty acid factory: If mycobacterial FAS are specifically inhibited, the pathogen's proliferation can be stopped—and this without affecting the fatty acid factory in [human cells](#), since the two differ sufficiently in their three-dimensional architecture.

Shuttle through the fatty acid factory

In yeast, the FAS has the shape of a barrel and consists of two domes with a total of six reaction chambers. Just like its human counterpart, it forms fatty acids, mainly palmitic acid, from different molecular groups in seven individual reaction steps. Each of these steps is catalyzed by its own enzyme at a different part of the fatty acid factory. Therefore, the

fatty acids must be transported from one enzyme to the next within the FAS. This task is performed by a molecular shuttle, the so-called acyl carrier protein (ACP). "We were particularly interested in understanding how this shuttling mechanism through the intricate FAS reaction chamber labyrinth works," project leader Chari says.

It actually took six years of work and two doctoral theses to answer this question—the results came as a big surprise to the researchers. Ph.D. student Kashish Singh remembers the moment of shock when presenting the first results to Ashwin Chari: "Ashwin immediately saw that our purified FAS contained an additional subunit." His colleague Benjamin Graf adds: "Our first thought was that the sample was contaminated and the whole effort was futile."

First regulator of fatty acid synthase

But Chari interpreted the results of his doctoral students differently: What if the building block is not an impurity at all, but a previously unknown, integral part of the FAS? After two more years of hard work, it was clear: The building block indeed belongs to the FAS. The researchers from Göttingen gave it the name gamma subunit. "With the harsher purification methods used so far, it probably was dissociated from the FAS, which probably explains how the gamma subunit was overlooked in the many decades of FAS research," Chari comments.

The next challenge for the Ph.D. students was to solve the three-dimensional structures of the FAS with and without gamma subunit to elucidate the function of this component. To do this, Graf and Singh combined X-ray structure analyses with cryo-electron microscopy. "The lengthy experiments have paid off. We were able to prove that the gamma subunit aids in the initial step of fatty acid production, the subunit resets the fatty acid factory to the starting position. From this state, fatty acid production can start and the gamma subunit defines the

functional compartment within FAS. In doing so, it changes the FAS structure in such a way that the ACP shuttle's path is much shorter," explains Max Planck Director Stark.

Benefits for medicine and biotechnology

The understanding of FAS activity control is an important breakthrough in research into fatty acid synthase. "Our findings open up new possibilities to enzymatically modify FAS in yeasts or to develop novel active compounds in the future that inhibit the fatty acid biosynthetic factory in mycobacteria. This could make FAS an even better starting point in the fight against this infectious disease," Chari stresses. New therapeutic approaches are increasingly important because there is a growing number of resistant tuberculosis pathogens. According to the World Health Organisation (WHO), around nine million people worldwide are infected with [tuberculosis](#) every year, around 1.4 million die each year as a result of the disease.

The improved methods developed by the researchers in Göttingen could also lead to new insights into FAS function in human cells, which could possibly be used in the fight against cancer, which require a lot of energy for their rapid growth. Many tumor types have far more fatty acid biosynthetic factories for this purpose than normal body cells. Reducing their fatty acid production could also inhibit proliferation of cancer cells.

The researchers led by Stark and Chari see further important applications in biotechnology. Fatty acids are components of cosmetics, soaps, and flavorings, but they are also contained in active pharmaceutical ingredients and biofuels. For the researchers, there are chances to produce fatty acids more sustainably: "Up to now, the fatty acids required for this purpose have mainly been produced chemically from crude oil or extracted laboriously from oil-containing plants. Yeast cells with tailor-made fatty acid factories could produce [fatty acids](#) with

the desired properties. These could replace fossil fuels in the future," reports Chari.

More information: Kashish Singh et al, Discovery of a Regulatory Subunit of the Yeast Fatty Acid Synthase, *Cell* (2020). [DOI: 10.1016/j.cell.2020.02.034](https://doi.org/10.1016/j.cell.2020.02.034)

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