New enzyme discovery may help improve drugs against cancer, diabetes and obesity

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A new study reveals that several drugs for treating haematological cancers are less effective than expected in inhibiting a special enzyme. Researchers have also identified new lead compounds that could potentially improve existing treatments and pave the way for new drugs against diabetes and obesity.

Almost all medical treatments are based on drugs that inhibit the activity of proteins in the body, leaving them unable to contribute to the development of such things as tumours, inflammatory diseases or metabolic disorders such as diabetes and obesity.

A number of drugs that target a group of proteins—the so-called HDAC enzymes—have attracted significant attention in recent years from researchers and drug developers, because they contribute to the development of resistance towards cancer treatments. New research has demonstrated that they also play a crucial role in a whole range of other diseases that are due to dysregulation of human genes.

An organic chemistry research team at the Faculty of Health and Medical Sciences, University of Copenhagen, has been investigating all the 11 HDAC enzymes expressed in human cells to develop specific molecules that can bind to the enzymes and block their activity in the body.

In a study just published in *Cell Chemical Biology*, the researchers carried out a wide range of tests using chemically designed molecules to reveal

the activities of HDAC enzymes and provide insights into their function at the molecular level. To their great surprise, they made a number of new, undescribed discoveries related to the HDAC11 enzyme.

"We have found a handle that will enable the identification of new inhibitors and this could potentially play a vital role in the development of drugs to treat several diseases," says Prof. Christian Adam Olsen, Center for Biopharmaceuticals at the University of Copenhagen.

The study shows that HDAC11 can cleave unexpected modifications on the surface of proteins. Proteins consist of long chains of 20 different amino acids in different sequences produced by the ribosome. The surfaces of proteins are also subsequently chemically modified in cells. It turns out now that HDAC11 affects specific variants of these modifications. By constructing chemical molecules that can bind to and regulate HDAC11, researchers can inhibit disease-causing mechanisms and the body's production of damaged cells.

Poor efficacy of approved drugs

As part of the study, the researchers investigated a range of existing drugs for treating haematological cancers, including leukaemia and lymphoma, and other well known HDAC inhibitors. Surprisingly, it turned out that several of the existing inhibitors were unable to block the newly-discovered enzymatic activity of HDAC11.

"This was the second major surprise in the study and suggests that the efficacy of HDAC-targeting drugs against the HDAC11 enzyme should be reassessed. For a long time, many HDAC inhibitors were believed to affect HDAC11 but we now have to question that. On the other hand, we have identified potent inhibitors from our compound library that we can use as the starting point for identifying new candidates with the potential for developing drugs," says Christian Adam Olsen.

Extensive drug target library

The study was based on extensive tests with the 11 human HDAC enzymes. Simultaneously with international research groups, the researchers developed chemically modified substrates for in vitro screening of enzymatic activity.

This has now resulted in an extensive library providing an overview of the enzymatic activities of HDACs against a variety of protein modifications in vitro. The researchers applied their discovery to develop the first efficient assay for determining the efficacy of drugs against HDAC11 in vitro, which may become important for the future development of drugs against a range of diseases such as diabetes, cancer, inflammatory disease, and autoimmune disease.

More information: Carlos Moreno-Yruela et al, Histone Deacetylase 11 Is an ε- N -Myristoyllysine Hydrolase, *Cell Chemical Biology* (2018). DOI: 10.1016/j.chembiol.2018.04.007

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