New small molecules for the treatment of autoinflammatory diseases

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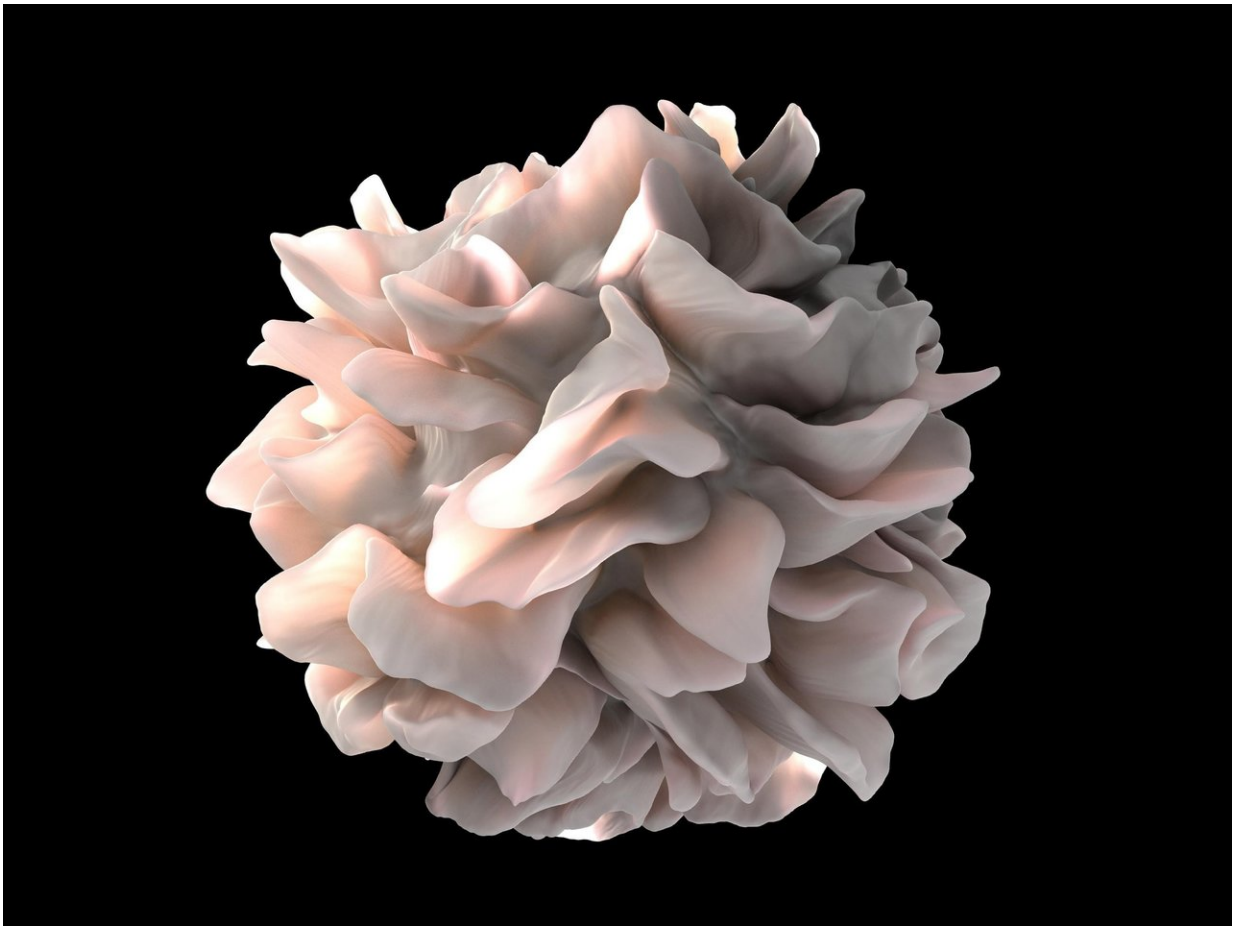

Artistic rendering of the surface of a human dendritic cell, one of the cells of the innate immune system. Credit: National Institutes of Health

EPFL scientists have discovered two small-molecule compound series that can effectively block a central pathway of the innate immune system, offering a promising new way for treating autoinflammatory diseases. The study is published in *Nature*.

The innate immune system is the first line of defense, with cells that quickly identify "foreign" motifs from viruses and bacteria and mount up a counterattack to eliminate them. As a key strategy to sense the presence of pathogens, the cells of the innate immune system use receptors that can identify microbial DNA and in turn activate a protein called STING (STimulator of Interferon Genes). Once activated, STING turns on genes that help cells fight off the infecting pathogen.

Nonetheless, the innate immune system can turn against the body itself, causing a number of diseases, which are referred to as autoinflammatory. But even though the molecules involved in the innate immune system are well studied, developing drugs that act on specific molecules of interest is still a big challenge.

Now, the lab of Andrea Ablasser at EPFL has discovered first-in-class compounds that specifically bind STING and effectively block its activity. The team used a screening assay to find molecules that can suppress STING-mediated cellular activation. From these they extracted two separate compound series that can block STING, both in human and in mouse cells.

To find out the compounds' mechanism of action, the researchers painstakingly mutated several of the amino acids that make up STING in order to find out which ones are targeted by the compounds. Doing so, the scientists identified a conserved transmembrane cysteine, which binds to the compounds irreversibly. As a consequence of this interaction, this particular cysteine residue can no longer undergo palmitoylation – a post-translational modification that attaches a fatty

acid (palmitic acid) to STING.

Although we don't know exactly how this chemical process connects to the activity of STING, the scientists observed that when STING was activated in the course of their experiments, it assembled into multimeric clusters – a well-known effect of palmitoylation. This observation adds evidence that palmitoylation is required for STING to perform its role during innate immune responses, presenting another potential target for blocking STING in the context of autoinflammatory disease.

Finally, the team carried out proof-of-concept pre-clinical studies to test the effect of the compounds on actual autoinflammatory diseases. For this, the scientists used the compounds to treat mice with mutations that constitutively activate STING, thereby producing a type of autoinflammatory disease similar to some seen in humans.

In an exciting finding, treatment with either compound class significantly reduced key pathogenic features in mice. Of importance, an in vitro test on cultured human cells with these small-molecules also showed efficacy to block the human version of STING further supporting therapeutical potential of these compounds in humans. However, confirmation of this effect would require formal clinical trials.

The discovered compounds are described as "small molecules", which is a term used for molecules with low molecular weight and up to a nanometer in size. In fact, most drugs are small molecules, meaning that the discovered compounds show promise for drug development.

"Our work uncovered an unexpected mechanism to target STING and provided the first proof-of-concept that anti-STING therapies are efficacious in autoinflammatory disease," says Andrea Ablasser. "Beyond specific monogenic autoinflammatory syndromes, the innate immune system is implicated in even broader 'inflammatory' conditions,

so we are excited to learn more about the role of STING in human diseases."

More information: Simone M. Haag et al. Targeting STING with covalent small-molecule inhibitors, *Nature* (2018). DOI: 10.1038/s41586-018-0287-8

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