Medical Xpress

On the trail of rare genetic disease, scientists uncover key immune regulator

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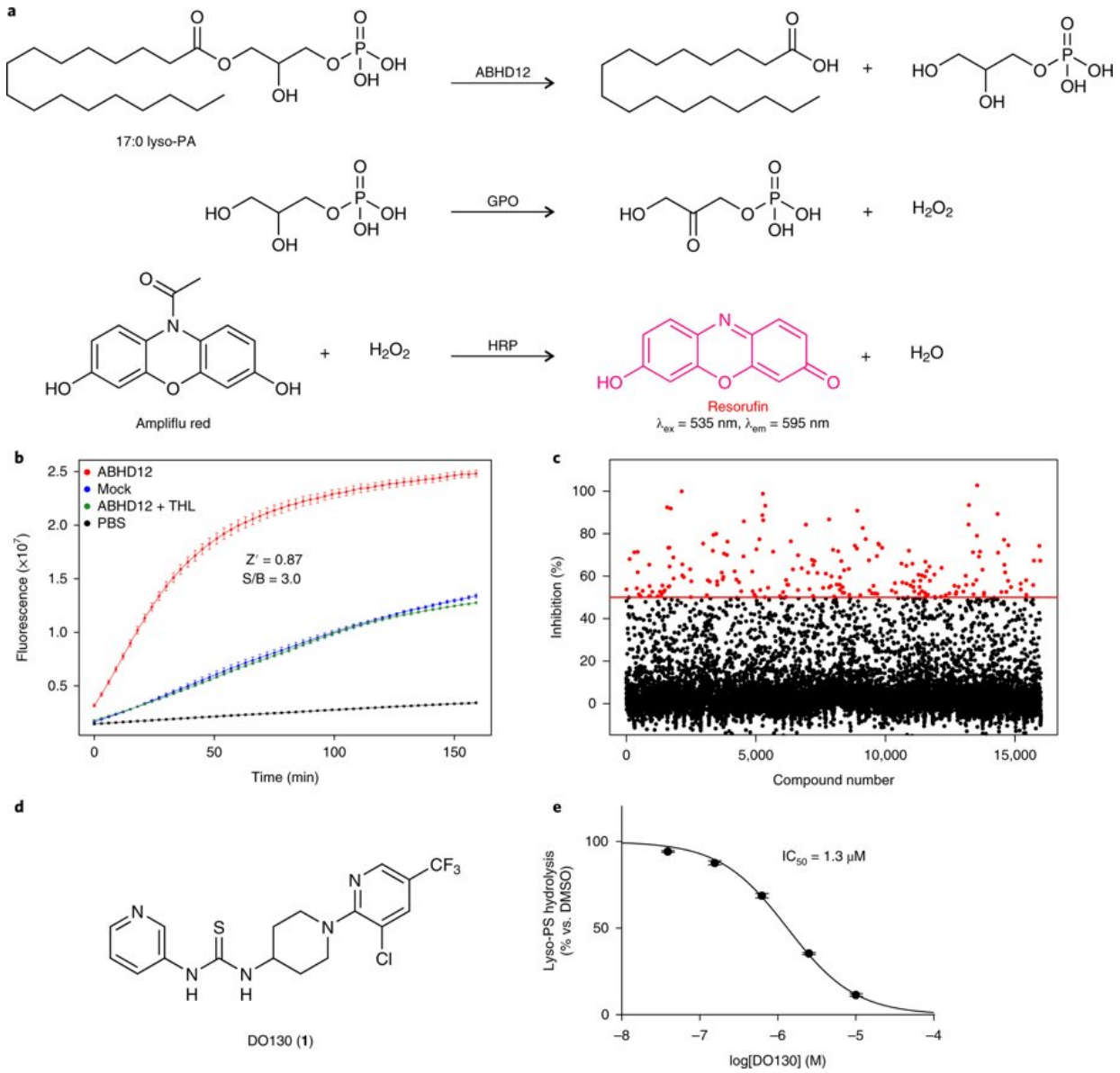

a, An enzyme-coupled assay that begins with ABHD12-mediated hydrolysis of

17:0 lyso-PA, which is followed by glycerol-3-phosphate oxidase (GPO)-mediated generation of H2O2, and culminates in the horseradish peroxidase (HRP)-mediated production of the fluorescent compound resorufin. b, Kinetic performance of the enzyme-coupled HTS assay with membrane lysates from ABHD12- or mock-transfected HEK293T cells. The Z′ and S/B values at 45 min were 0.87 and 3.0, respectively. THL (10 μM) was used as a control ABHD12 inhibitor. c, Screening data for the Maybridge HitFinder collection of 16,0000 compounds. Compounds showing > 50% inhibition are marked in red (198 total). The screen was performed once. d, Structure of the hit compound DO130. e, IC50 value for inhibition of lyso-PS hydrolysis activity of ABHD12 by DO130 measured using ABHD12-transfected cell lysates with 17:1 lyso-PS substrate (100 μM, 20 min, 37 °C). Data represent average values ± s.d. (n = 3 independent experiments). Credit: *Nature Chemical Biology* (2018). DOI: 10.1038/s41589-018-0155-8

Scientists at Scripps Research have found an important immune system-regulating protein that in principle could be targeted to treat cancers and chronic viral infections.

The scientists, in a study published November 12 in *Nature Chemical Biology*, set out to determine the function of a protein, ABHD12, whose absence causes a rare genetic disease featuring a host of brain and nerve problems.

The researchers found that ABHD12 normally acts as a powerful "brake" on the immune system to keep it from becoming harmfully overactive. Mice engineered without the protein have signs of elevated inflammation, and their immune systems are more likely to overreact to a viral infection.

The discovery suggests that the absence of ABHD12 in people with mutant versions of its gene may cause neurological disease at least in

part via excessive immune activity. It also indicates that ABHD12 may be a useful target for drugs that boost the immune system—for example against cancers and viruses that normally persist by shutting down people's immune defenses.

"This is a good example of how the study of a rare genetic disease can reveal a pathway that plays a key role in human biology," says study co-senior author Benjamin Cravatt, professor and chair of the Department of Chemical Physiology at Scripps Research.

The rare disease in this case is a mix of progressive brain, peripheral nerve, and eye problems that scientists have given the acronym PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataract). Since 2010, researchers have known that PHARC is caused by gene mutations that prevent ABHD12 from being made. But the normal function—or functions—of ABHD12, and the precise reasons its absence causes disease, have been unclear.

The Cravatt laboratory, in a 2013 study, engineered "knockout" mice that lack the ABHD12 gene, and determined that the ABHD12 protein is an enzyme that normally breaks down lysophospholipids—fat-related molecules that include lyso-PS, an important stimulator of immune activity. In the new study, Cravatt's team collaborated with researchers at Abide Therapeutics to extend their work on ABHD12 by developing a compound that selectively inhibits the enzyme's function.

"The idea was to use this inhibitor to disrupt ABHD12 in otherwise normal adult mice, and compare the effects to what we see in the ABHD12-knockout mice that never have a working copy of the enzyme," Cravatt says.

The team found that in adult mice, reducing ABHD12 activity with the inhibitor led to a rise in lyso-PS in immune cells called macrophages, as

well as in brain tissue. The rise wasn't as great as that seen in the ABHD12-knockout mice, and even four weeks of treatment with the inhibitor appeared to cause only slight hearing defects—nothing like the profound defects experienced by PHARC patients. However, in further experiments conducted by the laboratory of study co-senior author John Teijaro, an assistant professor in the Department of Immunology and Microbiology at Scripps Research, it was clear that the reduction in ABHD12 activity had a big effect on the mouse immune system.

Teijaro's team infected the inhibitor-treated mice with a virus called lymphocytic choriomeningitis virus (LCMV) clone 13, which can deactivate elements of the immune system to establish a persistent infection in its hosts. Ordinary mice infected with LCMV clone 13 typically have minor symptoms but take a long time to clear the infection.

Teijaro and colleagues found that the ABHD12-knockout mice, as well as the mice treated with the ABHD12 inhibitor, had immune responses that were much more vigorous and effective in clearing the virus, often excessively so.

"The enhanced mortality and lung pathology were striking in clone-13 infected mice following ABHD12 inhibition or deletion," Teijaro says.

The findings suggest several possibilities to investigate with future research. For example, the enhanced immune activity in the knockout and inhibitor-treated mice hints that the signs and symptoms of PHARC may have an immunological basis.

"It is now known that the immune system plays a big role in many brain diseases, including neurodegenerative diseases such as Alzheimer's and Parkinson's," Cravatt notes. "There have also been hints of immune involvement in developmental brain disorders such as autism and

schizophrenia."

He adds that if PHARC turns out to be caused in part by chronic brain and nerve inflammation, it might be treatable, if caught early enough, with anti-inflammatory or immune-suppressing drugs.

At the same time, treatments that target ABHD12, reducing its activity and stimulating the immune system, might have even broader use.

"The enhanced killer-T-cell activity we saw following ABHD12 deletion in the LCMV-infected mice suggests that blocking ABHD12 may enhance T-cell responses in immune suppressive environments such as chronic viral infections and cancers," Teijaro says.

"We're certainly eager to explore those possibilities," Cravatt says.

More information: Daisuke Ogasawara et al, Selective blockade of the lyso-PS lipase ABHD12 stimulates immune responses in vivo, *Nature Chemical Biology* (2018). DOI: 10.1038/s41589-018-0155-8

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