New anti-microbial compounds evade resistance with less toxicity

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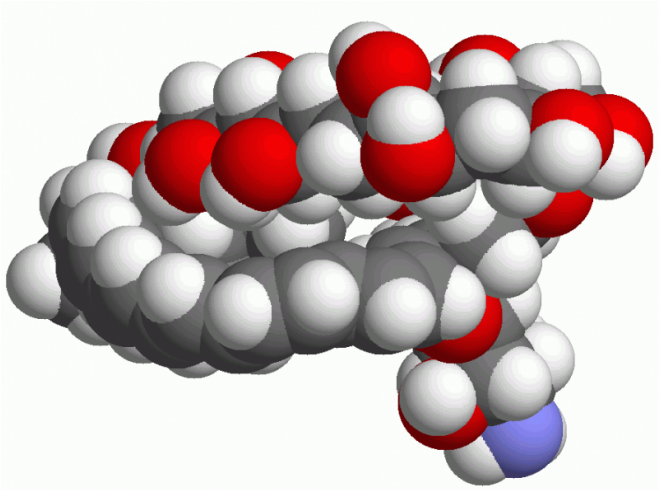

Space-filling model of amphotericin b. Credit: Wikipedia

New compounds that specifically attack fungal infections without attacking human cells could transform treatment for such infections and point the way to targeted medicines that evade antibiotic resistance.

Led by University of Illinois chemistry professor Martin D. Burke, a team of chemists, microbiologists and immunologists developed and tested several derivatives of the antifungal drug amphotericin B (pronounced am-foe-TARE-uh-sin B). They published their findings in the journal *Nature Chemical Biology*.

Amphotericin B is doctors' last, best defense against life-threatening fungal infections that invade a patient's blood and tissues, said Burke, who also is a medical doctor and a Howard Hughes Medical Institute Early Career Scientist. In half a century of use, amphotericin has yet to be overcome by new resistant strains of pathogens.

"The problem with this drug is that it is also highly toxic, particularly to the kidneys, and this limits the dose that can be given to a patient. As a result, invasive fungal infections still carry a mortality rate of about 50 percent, resulting in more than 1.5 million deaths each year - more than malaria or tuberculosis," said Burke.

Burke's group previously discovered that amphotericin B kills yeast and fungi by targeting a particular lipid molecule essential to the microbe's physiology, which is what makes it such an effective treatment, but it also binds to cholesterol in humans, which is thought to be what makes it so toxic.

In the new paper, Burke's group performed three simple chemical steps to convert amphotericin B to compounds that would bind more specifically to the lipid in fungi but not to cholesterol. They found particular derivatives that were extremely effective in killing invasive yeast infections in mice, but without the mice showing any signs of toxicity - even at much higher doses than a fatal dose of amphotericin B.

The researchers were concerned that because the drugs acted so specifically, resistant strains might emerge much faster. However, even when trying to generate mutations that would make yeast resistant, the researchers found that the derivatives were as elusive to resistance as the original amphotericin B, thus proving that targeted drugs and low resistance are not mutually exclusive.

"It has long been suspected that the unique capacity for amphotericin B to evade new resistance and its exceptional toxicity were inextricably linked," Burke said. "We were surprised and very gratified to find that these derivatives are no more vulnerable to resistance than amphotericin B, which has evaded new resistance development in patients for more than half a century."

"Learning more about basic chemical processes

paves the way for medical advances," said Jon Lorsch, the director of the National Institutes of Health's National Institute of General Medical Sciences, which partially funded the research. "In this elegant example, detailed knowledge of how a drug interacts with its target has pointed not only to possible improvements in our ability to treat life-threatening fungal infections, but also to a new approach for designing antimicrobial drugs."

Since amphotericin B is manufactured in mass quantities, the new compounds also could be made on a large scale. REVOLUTION Medicines, a company Burke co-founded, has licensed the compounds to develop optimal drug candidates and to pursue clinical studies.

Burke hopes that this method of tweaking naturally occurring compounds to make them more specific and less toxic not only produces better therapies for life-threatening fungal infections, but also helps in the development of other medications that circumvent resistance.

"More broadly, these results suggest that binding microbial-specific lipids that are critical for microbial physiology could represent a more general path to nontoxic yet resistance-evasive antimicrobial agents," Burke said.

More information: Nontoxic antimicrobials that evade drug resistance, *Nature Chemical Biology*, 10.1038/nchembio.1821

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