Medical Xpress

Molecule enhances copper's lethal punch against microbes

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Harnessing a natural process in the body that pumps lethal doses of copper to fungi and bacteria shows promise as a new way to kill infectious microbes, a team of scientists at Duke University report.

Publishing in the July 31, 2014, issue of the journal *Chemistry & Biology*, the researchers describe a way of exploiting the unique chemical response from the body's immune system to attack pathogens using copper, long known for its antimicrobial properties, in a way that minimizes harm to the rest of the body.

The findings in cell and animal models represent progress in developing broad-spectrum antimicrobial agents on the basis of copper biology – a much-needed advance in the face of escalating antibiotic resistance and lethal fungal infections.

"There is a clear need for new strategies for antimicrobial therapies," said senior author Dennis J. Thiele, Ph.D., the George Barth Geller Professor of Pharmacology and Cancer Biology and of Biochemistry at Duke University School of Medicine. "Copper, while essential, can be toxic when mismanaged by the body, but our work demonstrates that we can activate the metal's antimicrobial potential in a targeted fashion that focuses on the immune cells and avoids copper imbalance throughout the body."

Thiele, who has studied the biology of copper for more than 30 years, teamed with Katherine J. Franz, Ph.D., the Alexander F. Hehmeyer

Associate Professor of Chemistry at Duke, to use a small molecule previously created in the Franz lab that essentially escorts additional copper to specialized chambers within immune cells called macrophages.

Faced with fungal or bacterial infections, macrophages ingest and attempt to destroy the pathogens by locking them in tiny death chambers and unleashing an oxidative burst of hydrogen peroxide, nitric oxide and other poisons, including copper. But both fungi and bacteria deploy resistance mechanisms to the chemical onslaught in the macrophage compartments.

Thiele, Franz and colleagues used a clever chemical trick that takes advantage of this oxidative onslaught to unleash the active molecule selectively in the macrophage death chambers. The molecule then synergizes with copper already present in the cells to kill microbial pathogens. The strategy is designed to protect healthy cells by avoiding copper binding in cells that have not been infected.

"This provides a strategy for the development of compounds that exploit the activated immune response and override the copper detoxification machinery in fungal and bacterial pathogens to boost the body's own antimicrobial activity," Franz said.

Thiele said future studies will focus on enhancing the molecule's drug-like properties to optimize its ability to fight additional fungal and bacterial infections in animal models. They are also continuing to explore how the molecule works, and whether related molecules can deliver additional metal payloads, including silver, which also has antimicrobial properties.

Provided by Duke University Medical Center