Scientists discover potential therapy for human copper metabolism disorders

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Individuals with defects in copper metabolism may soon have more targeted treatment options thanks to a discovery by a research team led by Dr. Vishal Gohil of Texas A&M AgriLife Research in College Station.

A paper in the *Proceedings of the National Academy of Sciences* reports that an investigational anticancer-drug, elesclomol, can restore the production of cytochrome oxidase protein complex, a critical copper-dependent enzyme required for mitochondrial energy production.

The discovery is vital since copper is an essential trace metal necessary for survival. Copper is found in all body tissues and plays a critical role in a variety of physiological processes, including energy production, detoxification of harmful free radicals, connective tissue maturation, neurotransmitter biosynthesis and brain development.

Copper metabolism deficiencies have been linked to genetic disorders such as Menkes disease, which affects infants and young children and results in deterioration of the nervous system and failure to fully develop.

The research was led by Gohil, an associate professor in the department of biochemistry and biophysics at Texas A&M University in College Station, and his graduate student, Shivatheja Soma, who worked collaboratively with scientists at the Marine Biological Laboratory, the University of Maryland, the University of Saskatchewan in Canada and the Department of Drug Discovery and Biomedical Sciences in South Carolina.

"Copper is an essential micronutrient required for mitochondrial energy production," Gohil said. "Inherited mutations that prevent copper delivery to a key mitochondrial enzyme perturb energy production and result in fatal mitochondrial disease. Currently, no therapy exists for these disorders."

Gohil said a prior attempt to treat patients with these mutations by direct copper supplementation was not successful, possibly because of inefficient copper delivery to the mitochondria.

"Through a targeted search for copper-binding compounds, we identified elesclomol, an investigational anti-cancer drug, as the most efficient copper delivery agent," he said.

The study utilized multiple model organisms to test the efficacy of elesclomol in rescuing copper deficiency. In particular, a zebrafish model of copper deficiency developed by Dr. Andrew Latimer, a research scientist at the Marine Biological Laboratory in Massachusetts, was vital in showing the efficacy of elesclomol in a vertebrate animal. Additionally, the authors directly demonstrated the therapeutic potential of elesclomol in human patient cells with genetic mutations that impair copper delivery to cytochrome oxidase.

The research involved testing several copper-binding pharmacological agents for their ability to restore mitochondrial function in a yeast model. Among these compounds, they found elesclomol was unique in that it was efficacious at low nanomolar concentrations without exhibiting overt toxicity at higher concentrations.

According to the scientists, these findings reveal that elesclomol can mimic the missing transporters of copper, which provide the potential opportunity to treat human disorders of copper metabolism.

"Elesclomol has undergone multiple human clinical trials, thus our findings offer an exciting possibility of repurposing this anti-cancer drug for the treatment of copper metabolism disorders," Gohil said.

More information: Shivatheja Soma et al. Elesclomol restores mitochondrial function in genetic models of copper deficiency, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1806296115

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