Researchers discover family of natural compounds that selectively kill parasites

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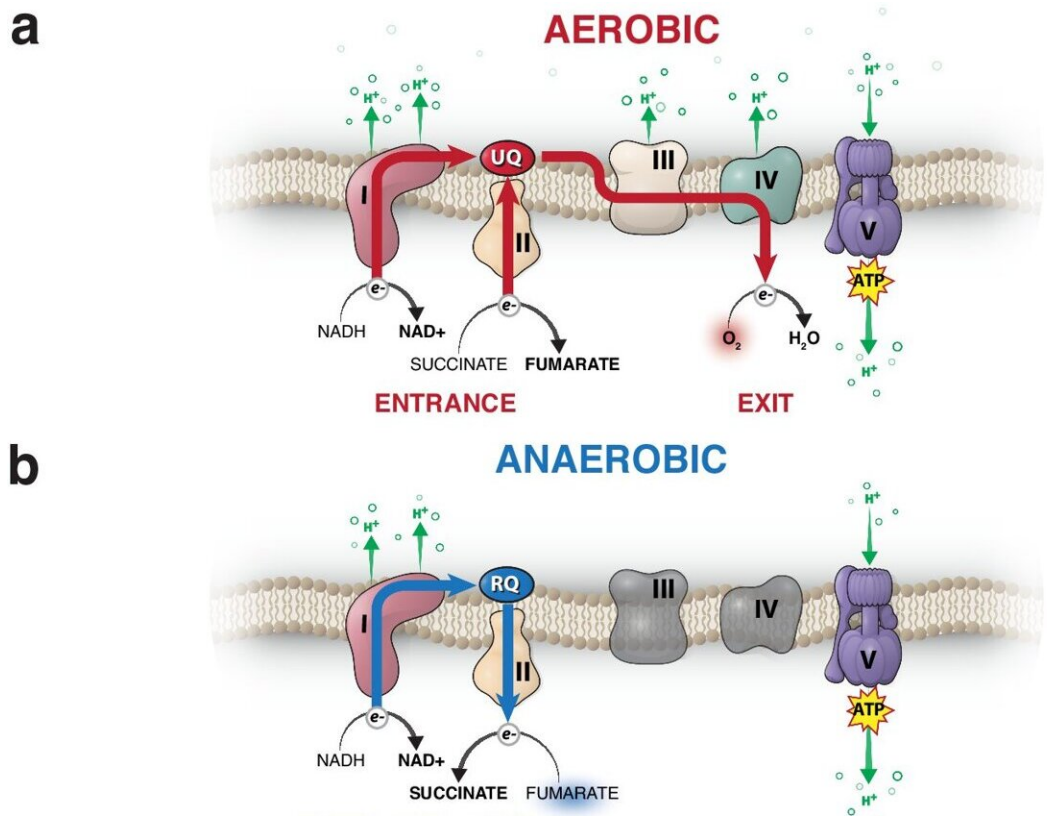

The distinct rhodoquinone-dependent metabolism of parasitic helminths is an attractive target for anthelmintic development. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-47331-3

An international team led by researchers at the University of Toronto has found a family of natural compounds with potential as new and more

effective treatments for parasitic worms. The compounds stall the unique metabolic process that worms use to survive in the human gut.

Parasitic worms transmitted through soil wreak havoc in developing countries in the tropics. Infection by these parasites leads to malaise, weakness, malnutrition and other debilitating symptoms, and can cause developmental defects in children and impair their growth.

"Soil-transmitted parasitic worms infect over one billion people around the world, typically in low-income communities of developing countries without comprehensive health care and infrastructure for sanitation," said Taylor Davie, first author on the study and Ph.D. student at U of T's Donnelly Center for Cellular and Biomolecular Research. "Parasites are becoming less susceptible to the few anthelmintic drugs available, so there's an urgent need to find new compounds."

The study is published in the journal *Nature Communications*.

Many parasitic worm species live out a large portion of their life cycle inside a human host. To adapt to the environmental conditions of the gut, particularly a lack of oxygen, the parasite switches to a type of metabolism that depends on a molecule called rhodoquinone (RQ).

The parasite can survive inside its human host for many months using RQ-dependent metabolism.

The research team chose to target the adaptive metabolic process of the parasitic worm because RQ is only present in the parasite's system—humans do not produce or use RQ. Therefore, compounds that can regulate the molecule's production or activity would selectively kill the parasite, with no harm done to the human host.

The researchers conducted a screen of natural compounds isolated from

plants, fungi and bacteria on the model organism C. elegans. While it is not a parasite, this worm also depends on RQ for metabolism when oxygen is not available.

"This is the first time that we have been able to screen for drugs that specifically target the unusual metabolism of these parasites," said Andrew Fraser, principal investigator on the study and professor of molecular genetics at the Donnelly Center and the Temerty Faculty of Medicine.

"The screen was only possible because of recent progress made by our group and others in using C. elegans to study RQ-dependent metabolism, and our collaboration with RIKEN, one of Japan's biggest research agencies. We screened their world-class collection of 25,000 natural compounds, resulting in our discovery of a family of benzimidazole compounds that kills worms relying on this type of metabolism."

The researchers suggest a multi-dose regimen using the newly discovered family of compounds to treat parasitic worms. While a single-dose treatment is easier to facilitate in mass drug administration programs, a longer treatment program would eliminate the parasite more effectively.

"We are very pleased with the results of the study, which made use of our library," said Hiroyuki Osada, professor of pharmacy at the University of Shizuoka and group director of the Chemical Biology Research Group at the RIKEN Center for Sustainable Resource Science.

"The study shows the power of the screening approach, allowing researchers in this case to search through a very large number of molecules within a focused collection of natural products. Screens are very efficient, which is key for addressing urgent research questions of global relevance like this one."

Next steps for the research team are to refine the new class of inhibitors through additional in vivo testing with parasitic worms, which will be performed by the Keiser lab at the University of Basel in Switzerland, and to continue screening for compounds that inhibit RQ.

"This study is just the beginning," said Fraser. "We have found several other very powerful compounds that affect this metabolism, including, for the first time, a compound that blocks the ability of the worms to make RQ. We hope our screens will deliver drugs to treat major pathogens around the world."

More information: Taylor Davie et al, Identification of a family of species-selective complex I inhibitors as potential anthelmintics, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47331-3

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