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Gene expression studies reveal drug combination effective against schistosomiasis

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Schistosomiasis is a neglected tropical disease caused by parasitic worms endemic in parts of Africa, Southeast Asia and Central and South America. It is currently treated by the drug praziquantel which, while both effective and cost efficient, does not prevent reinfection after the disease has cleared. Praziquantel is the only current treatment, and while no resistance has been observed in humans, animal models predict that repeated rounds of treatment may lead to the evolution of drug resistance. It is therefore important to explore both alternative treatments and synergistic therapies to expand the lifetime and effectiveness of the praziquantel treatment.

Researchers from the University of Sao Paulo used a gene expression microarray to explore how the gene expression of adult worms was affected by a sub-lethal dose of praziquantel. Previous research had found differences between male and female worms, and the researchers found further differences between females from mixed-sex infection either joined to males in a mating pair, or unpaired. Females from mixed-sex infections unpaired with males were more likely to down-regulate their gene expression in response to praziquantel (77% of genes down-regulated). Conversely, paired females were more likely to up-regulate their genes in response to treatment, with 98% of affected genes up-regulated.

The researchers also looked for genes that could act as potential targets for new therapies. They found a promising target in a gene affected in all the worms that coded for a type of proton pump. The proton pump was

homologous to a protein found in humans and targeted by the proton pump inhibitor drug omeprazole. They therefore tested the effect of treating parasites with either sub-lethal doses of praziquantel, omeprazole alone, or a combination of both drugs.

While the omeprazole alone did not kill the parasites the researchers found that combining it with sub-lethal doses of praziquantel killed more parasites than praziquantel alone. It is likely that by inhibiting the increased proton pump activity, related to its increased expression caused by praziquantel, the omeprazole was able to finish off already stressed parasites and act as an adjuvant to the current therapy. Given the reach of Schistosomiasis, and the dependence on praziquantel as the sole treatment, it is encouraging to see that options exist to increase the capabilities and improve the lifespan as an effective treatment.

More information: *PLOS Neglected Tropical Diseases*, dx.plos.org/10.1371/journal.pntd.0004086

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