A member of the aldoketo reductase family confers methotrexate resistance in *Leishmania*

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Methotrexate (MTX)-resistant mutants of the parasitic protozoan *Leishmania* have been used as models for the mechanism and genetic basis of drug resistance in trypanosomatids and other cells. Three resistance mechanisms to MTX, a dihydrofolate reductase inhibitor, have been described in *Leishmania*: decreased uptake and accumulation of MTX via the folate/MTX transporter, amplification and overexpression of the dihydrofolate reductase-thymidylate synthase gene, and extrachromosomal amplification of H region DNA. We have now identified \textit{hmtx} as the H region gene conferring MTX resistance using a transfection-based approach. Data base searches show that the predicted HMTX protein is related to members of the polyol dehydrogenase/carbonyl reductase family of aldoketo reductases, whose substrates include polyols, quinones, steroids, prostaglandins, fatty acids, and pterins. We therefore propose that HMTX is also an oxidoreductase and suggest several biochemical mechanisms of resistance in *Leishmania* that could be exploited in the design of parasite-specific inhibitors.

Note: \textit{hmtx} has been renamed PTR1 (Pteridine reductase 1).
See Bello et al PNAS 91: 11442 (1994).