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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 *hmtx*^{r} as the H region gene conferring MTX resistance using a transfection-based approach. Data base searches show that the predicted HMTX^r 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^r 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: hmtx^r has been renamed PTR1 (Pteridine reductase 1).
See Bello et al PNAS 91: 11442 (1994).