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Adaptations in the energy metabolism of parasites

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For this thesis fundamental research was performed on the metabolic adaptations found in parasites. Studying the adaptations in parasite metabolisms leads to a better understanding of parasite bioenergetics and can also result in the identification of new anti-parasitic drug targets. We focussed on parasite specific adaptations in energy metabolism in the mitochondria of *Fasciola hepatica* and *Trypanosoma brucei*, and in the hydrogenosomes of *Trichomonas vaginalis*.

As many parasites produce acetate as an end product of their energy metabolism, whereas their mammalian hosts do not, acetate production might provide an interesting drug target in many parasites. Recently, the acetate-producing enzyme present in the unicellular parasite *T. brucei* was identified. Unexpectedly no homolog of this *T. brucei* enzyme is present in the completely sequenced genome of *T. vaginalis*. However, we did identify another, unrelated, candidate enzyme in this genome, and proved this gene to be the acetate-producing enzyme in the hydrogenosomes of *T. vaginalis*. Furthermore, we showed that a homolog of this gene is also involved in acetate production in the parasitic worm *F. hepatica* and that these enzymes are conserved in many different types of parasites, but are absent in mammals. Therefore, we identified a new drug target, with the potential to target many parasitic infections.

A recently reported adaptation in the acetate-forming, aerobic mitochondria of procyclic *T. brucei* is the absence of a functional Krebs cycle. This recent finding is, however, not compatible with older literature. The discrepancy might be explained by the fact that older studies often used fresh isolates of *T. brucei*, whereas recent reports use long-term *in vitro* cultured trypanosomes. We studied glucose catabolism in procyclic trypanosomes directly after isolation from their natural environment, the midgut of the tsetse fly, as well as in a *T. brucei* strain that has only been passaged a few times since its field-isolation. These experiments confirmed the absence of a functional Krebs cycle in procyclic trypanosomes. Furthermore, they demonstrated that bloodstream form short-stumpy *T. brucei* produce acetate in their mitochondria. This mitochondrial acetate is apparently a pre-adaptation of these parasites to their next host, the tsetse fly.

A different type of metabolic adaptation is found in the acetate producing, anaerobically functioning, mitochondria of adult *F. hepatica* worms, which use an alternative electron acceptor named rhodoquinone (RQ). RQ is found in relatively few species, among which many parasitic worms, and is not present in mammals. Since the biosynthetic pathway of this electron acceptor was unexplored and presumably involves at least one parasite specific enzyme, we performed studies on the biosynthetic pathway of RQ. This resulted in the identification of two enzymes involved in RQ biosynthesis. Both of these enzymes are also required for the biosynthesis of the structurally similar quinone ubiquinone (UQ). UQ is present in nearly all organisms, including mammals. Our studies provide the first evidence that RQ biosynthesis occurs via part of the biosynthetic pathway of UQ and show that demethoxy-ubiquinone (HQ) is the last common precursor for both these quinones.

