1982	Ph.D. - University of Heidelberg, Germany (Max Planck Institute for Medical Research, Heidelberg)
1982 - 1995	Staff Member - Institute of Biochemistry II, University of Heidelberg
1989	Habilitation in Biochemistry
1995 - 2003	Apl. Professor for Biochemistry - BZH
2002	Call for a professorship for Pharmaceutical Chemistry (Marburg), declined
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Luise Krauth-Siegel

The parasite-specific trypanothione redox metabolism

Goal

Aim of our work is to unravel the unique trypanothione-based thiol redox metabolism of trypanosomatids in atomic detail and to contribute to the development of new antiparasitic drugs on the basis of specific enzyme inhibitors and by identifying novel target molecules.

Background

Trypanosomatides, the causative agents of various tropical diseases, possess an unusual redox metabolism. The main non-protein thiol is the bis(glutathionyl)spermidine-conjugate trypanothione which is an essential metabolite for a wide variety of parasite pathways (Fig. 1; Krauth-Siegel and Leroux 2012).

Research Highlights

Dissecting the mechanism of trypanothione synthetase under *in vivo*-like conditions

All proteins of the trypanothione metabolism are indispensable for the viability of African trypanosomes. A final conclusion as to which protein plays a main role in the pathway control yet would need a reliable model based on the kinetic parameters of all enzymes obtained under conditions that reflect the milieu in which the pathway is operating. The kinetic analysis under such *in vivo*-like conditions together with computational modelling revealed that trypanothione synthetase follows a ter-reactant mechanism, releases the intermediate glutathionylspermidine between the two catalytic steps and undergoes both substrate and product inhibition suggesting a tight *in vivo* regulation (Leroux et al. 2013).

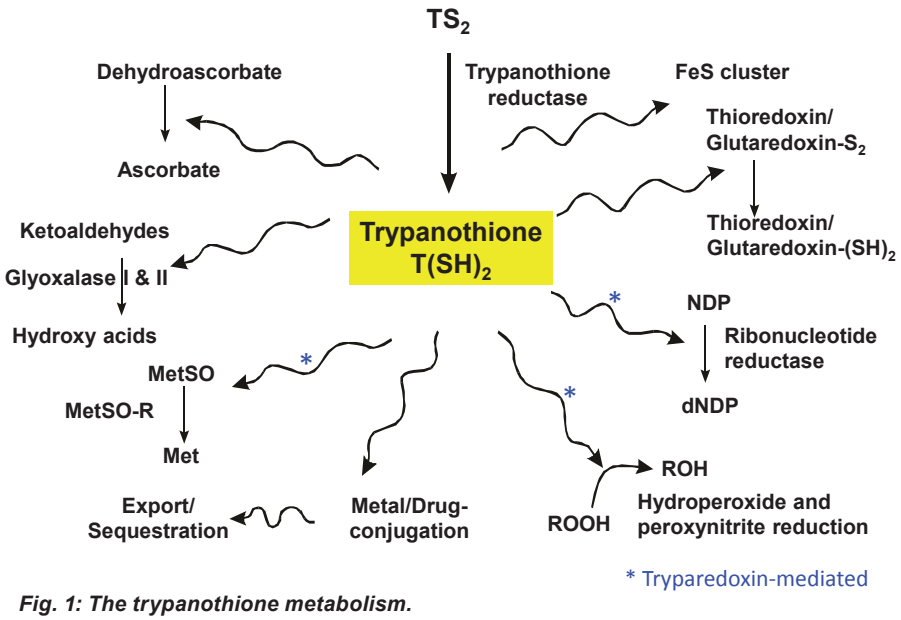

Fig. 1: The trypanothione metabolism.

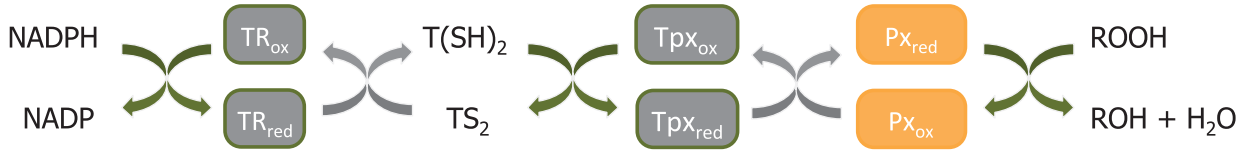

Fig. 2: Detoxification of hydroperoxides (ROOH) by the trypanothione redox cascade.

Detoxification of lipid hydroperoxides in trypanosomes

In *Trypanosoma brucei*, glutathione peroxidase-type (Px) enzymes, obtaining their reducing equivalents from the T(SH)$_2$/tryparedoxin (Tpx) system (Figs 1 and 2), are responsible for the detoxification of lipid hydroperoxides. Deletion of the individual px genes revealed that the cytosolic isoenzymes, but not the mitochondrial one, are essential. Parasites lacking the cytosolic peroxidases show an extremely rapid cell lysis (Fig. 3). Their proliferation, however, can fully be rescued by supplementing the medium with the vitamin E analog Trolox (Diechtierow and Krauth-Siegel 2011). Recently we could show that the cellular damage originates from disintegration of their lysosome (Hiller et al., submitted).

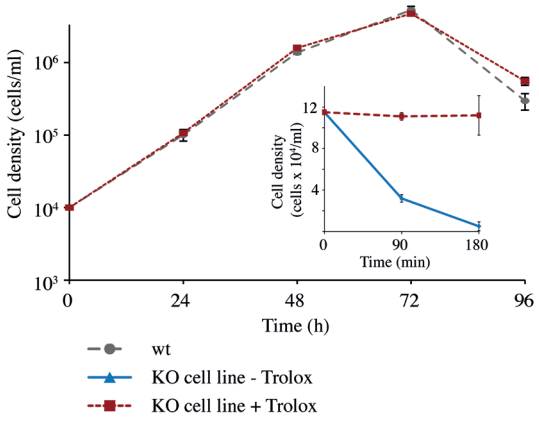

Fig. 3: Bloodstream T. brucei lacking the cytosolic peroxidases are highly sensitive to cell lysis.

The infective form of African trypanosomes requires lipoamide dehydrogenase for DNA synthesis

Lipoamide dehydrogenase (LipDH), a member of the FAD disulfide oxidoreductase family which also comprises TR, GR, and ThioR, is a component of four mitochondrial multienzyme complexes. Bloodstream *T. brucei* rely exclusively on glycolysis for energy supply. These parasites have an only rudimentary mitochondrion devoid of cytochromes and most enzymes of the citric acid cycle. Thus the role of LipDH in these cells remained elusive. We could show that deletion of *lipdh* resulted in cells with an absolute need for exogenous thymidine. This strongly suggests that bloodstream parasites require LipDH as component of the glycine cleavage complex which generates methylene-tetrahydrofolate for dTMP and thus DNA synthesis (Roldán et al. 2011).

Selected Publications 2011 - 2013

Leroux, A.L., Haanstra, J. R., Bakker, B. M. and Krauth-Siegel, R. L. (2013) Dissecting the catalytic mechanism of *Trypanosoma brucei* trypanothione synthetase by kinetic analysis and computational modelling, J. Biol. Chem. 288, 23751-23764.

Comini, M. A., Krauth-Siegel, R. L. and Bellanda, M. (2013) Mono- and dithiol glutaredoxins in the trypanothione-based redox metabolism of pathogenic trypanosomes. Antiox. Redox Sign. 19, 708-722.

Manta, B., Pavan, C., Sturlese, M., Medeiros, A., Crispo, M., Berndt, C., Krauth-Siegel, R. L., Bellanda, M. and Comini, M. A. (2013) Iron-sulfur cluster (ISC) binding by mitochondrial monothiol glutaredoxin-1 of *Trypanosoma brucei*: molecular basis of ISC coordination and relevance for parasite infectivity. Antiox. Redox Sign. 19, 665-682.

Krauth-Siegel, R. L. and Leroux, A. (2012) Low Molecular mass antioxidants in parasites. Antiox. Redox Sign. 17, 583-607.

Füller, F., Jehle, B., Putzker, K., Lewis, J. D. and Krauth-Siegel, R. L. (2012) High-throughput screening against the peroxidase cascade of African trypanosomes identifies antiparasitic compounds that inactivate tryparedoxin. J. Biol. Chem. 287, 8792-8802.

Diechtierow, M. and Krauth-Siegel, R. L. (2011) A tryparedoxin-dependent peroxidase protects African trypanosomes from membrane damage. Free Radic. Biol. Med. 51, 856-868.

Roldán, A., Comini, M. A., Crispo, M. and Krauth-Siegel, R. L. (2011) Lipoamide dehydrogenase is essential for both bloodstream and procyclic *Trypanosoma brucei*. Mol. Microbiol. 81, 623-639.

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