Universität Basel

Research Project

Molecular mechanisms of suramin resistance in Trypanosoma brucei

Third-party funded project

Project title Molecular mechanisms of suramin resistance in Trypanosoma brucei
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Project start 01.10.2019
Probable end 30.09.2023
Status Completed

Suramin is a hundred years old and still being used to treat the first stage of acute human sleeping sickness, caused by Trypanosoma brucei rhodesiense. Suramin is a fascinating molecule with a wide array of potential applications, from parasitic and viral diseases to cancer and autism. Suramin is also an enigmatic molecule: What are its targets in African trypanosomes? And how does it get into the trypanosomes in the first place? Due to its size and negative charge, suramin is likely imported via receptor-mediated endocytosis, and the receptor in T. brucei bloodstream forms is thought to be the invariant surface glycoprotein ISG75. Nevertheless, we have recently identified a variant surface glycoprotein, termed VSGSur, expression of which is sufficient to render T. brucei bloodstream forms 100-fold resistant to suramin. While VSGSur-mediated resistance is independent of ISG75, it is linked to the endocytosis of low density lipoprotein. Expression of VSGSur in T. brucei affects selected membrane receptors, impairing the endocytosis of LDL and of transferrin, but not of the trypanolytic factor or of VSG itself. Our findings support the model of two independent pathways for suramin endocytosis, via ISG75 or via the LDL receptor, whereby the latter is disturbed by VSGSur. Interestingly, further in vitro selection of VSGSur expressing trypanosomes with suramin yielded a VSGSur variant with several point mutations. This variant, termed VSGSupersur, causes even stronger suramin resistance than VSGSur when expressed in T. brucei. Selection for high-level suramin resistance combined with genomics also provided a new candidate for the intracellular target of suramin. The suramin-resistant trypanosomes became homozygous for a non-synonymous point mutation in a DNA helicase of T. brucei, and the same residue turned out to be mutated also in a suramin-resistant field isolate of T. evansi. DNA helicase is a known antiviral target of suramin but has so far not been implicated in the trypanocidal action of suramin. Here we propose to further dissect these promising leads, aiming to understand the molecular mechanisms of suramin action and resistance, and thereby identifying also the LDL receptor of T. brucei. The project is carried out in collaboration with Prof. Mark Field, University of Dundee.

Financed by
Swiss National Science Foundation (SNSF)

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