Intruder alert! Towards a systems-biology based counterstrike against infectious diseases without collateral damage

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A huge challenge in the combat of infectious diseases is to target the disease-causing agent without harming its human host. One approach is to find unique drug targets in the pathogen-specific proteome, but in eukaryotic pathogens those may be limited or the existing ones may not control a process that is vital for pathogen survival. Therefore we should expand the search for promising drug targets by elucidating network-based differences that convey a stronger effect of a drugin the pathogen than in the host.

Trypanosomabrucei is a eukaryotic parasite causing deadly diseases in human and cattle and that lives in the serum of the mammalian bloodstream. There, *T. brucei* can only generate ATP in glycolysis, making glycolysis a potent target pathway for antitrypanosomal drugs. Combining mathematical modeling and wet-lab experiments we have previously identified glucose transport as the enzyme with the highest flux control over trypanosome glycolysis. Indeed, glucose transport inhibitors killed trypanosomes. We found that parasites that were able to survive this treatment, started to rewire carbon metabolism. Unexpectedly, this adaptation even strengthened the potential of glucose transport as a drug target: glycolytic enzyme expression was decreased and targetable antigens appeared on its membrane. These anti-homeostatic adaptive responses of the parasitethus even lower the overall median lethal dose – or LD50 - of the drug.

But the challenge remains to combat the parasite inside the host. To address this we started with a comparison with its closest neighbor in the host: the red blood cell. Comparison of two similarly detailed kinetic models of glycolysis of the trypanosome and of the erythrocyte revealed that inhibitors of glucose transport that are competitive for glucose affect trypanosome glycolysis much stronger than glycolysis in the erythrocyte. We have developed co-culture experiments between trypanosomes and human erythrocytes that enables testing of differential effects. The experiments reveal that, even in a situation that is more favorable to the trypanosome, glucose transport inhibitors can selectively kill the trypanosome without affecting survival or metabolism of erythrocytes.

In conclusion, we show that selective killing of trypanosomes in the context of the host is possible even when we hit a shared targetwithin a pathway that is essential for parasite survival. This exemplifies that the arsenal of potential selective drug targets can be broadened beyond the pathogen-specific proteome.