Dynamic optimization of pathway regulation and cytoxicity prediction of metabolites in pathogenic fungi exploit the hidden potential of toxic intermediates as drug targets

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The understanding of metabolism and its regulation is crucial for a holistic comprehension of biological processes. However, the time dependency is often lowly resolved or completely neglected, but is important to recover the principles behind regulation. To fill those gaps, dynamic optimization has been used to identify principles shaping regulatory networks controlling metabolism by assuming optimality principles underlying pathway control [1, 2]. The modeling of a linear metabolic pathway with different kinetic properties and toxicity of metabolites lead us to principles validated by large scale metabolic data sets of various organisms. In our present study [3], we focus on the impact of toxic metabolites on the regulatory strategies controlling metabolic pathways. We found that toxic metabolites are controlled by a tight regulation of upstream enzymes preventing their accumulation, which changes the position of the mainly regulated enzyme. These findings can explain a sparse regulation by key enzymes at various positions of a pathway and not mainly at the first and last position, as observed previously [4, 2]. Our latest results suggest that these optimality principles are shared by bacteria as well as eukaryotes like the pathogenic fungi *Aspergillus fumigatus* or *Candida albicans*. Since there only few known compounds that impede growth of fungi while not affecting the human host, we created a framework to predict the cytoxicity of metabolites in fungal cells based on their structure to identify targets for antimicrobial interventions. Beyond this, we integrated the results with networks of the KEGG database to build a easy to use visualization of toxic metabolites in metabolic networks to identify drug targets. Together with our findings of optimality principles in pathway regulation, this provides a new avenue of drugs that induce self-poisoning based on the perturbation of highly regulated enzymes that prevent the accumulation of toxic metabolites.

References

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