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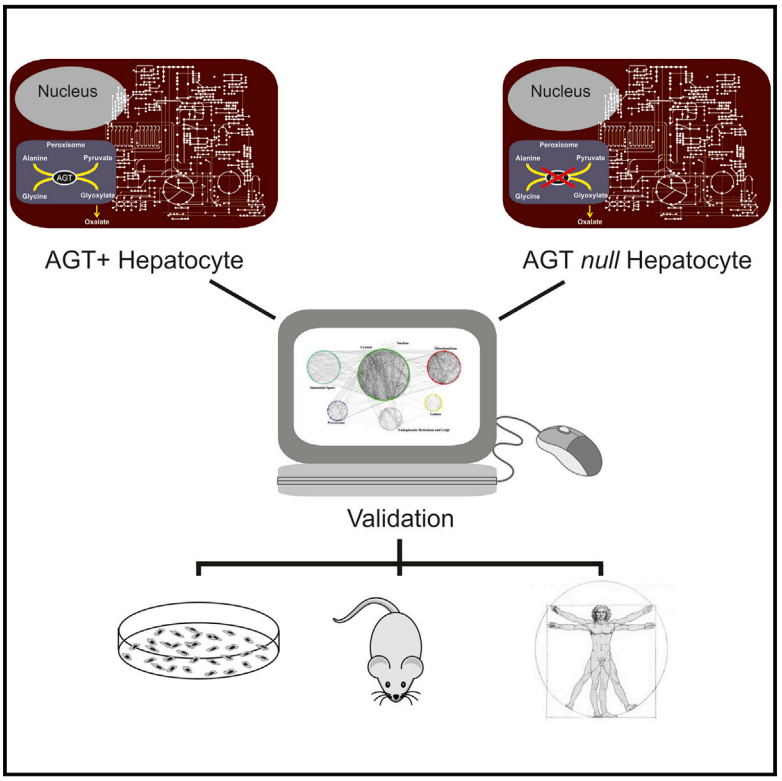
In Silico Modeling of Liver Metabolism in a Human Disease Reveals a Key Enzyme for Histidine and Histamine Homeostasis

Graphical Abstract



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In Brief

Pagliarini et al. use a computational model of liver metabolism to predict alterations caused by the loss of alanine:glyoxylate aminotransferase (AGT), resulting in primary hyperoxaluria type I (PH1). In addition to known disease biomarkers, the model predicts a reduction in histidine and histamine levels. GPT overexpression in PH1 mice normalizes histamine and oxalate levels.

Highlights

- In silico model of liver metabolism reveals global metabolic alterations in PH1
- Changes in amino acid metabolism in PH1 result in a reduction of histidine and histamine
- GPT overexpression normalizes histamine levels and reduces oxalate in PH1 mice

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In Silico Modeling of Liver Metabolism in a Human Disease Reveals a Key Enzyme for Histidine and Histamine Homeostasis

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SUMMARY

Primary hyperoxaluria type I (PH1) is an autosomal-recessive inborn error of liver metabolism caused by alanine:glyoxylate aminotransferase (AGT) deficiency. In silico modeling of liver metabolism in PH1 recapitulated accumulation of known biomarkers as well as alteration of histidine and histamine levels, which we confirmed in vitro, in vivo, and in PH1 patients. AGT-deficient mice showed decreased vascular permeability, a readout of in vivo histamine activity. Histamine reduction is most likely caused by increased catabolism of the histamine precursor histidine, triggered by rerouting of alanine flux from AGT to the glutamic-pyruvate transaminase (GPT, also known as the alanine-transaminase ALT). Alanine administration reduces histamine levels in wild-type mice, while overexpression of GPT in PH1 mice increases plasma histidine, normalizes histamine levels, restores vascular permeability, and decreases urinary oxalate levels. Our work demonstrates that genome-scale metabolic models are clinically relevant and can link genotype to phenotype in metabolic disorders.

INTRODUCTION

Metabolism is primarily or secondarily affected in several acquired and inherited human diseases. Characterization of the metabolic changes occurring in health and disease states has a wide range of implications, from elucidation of pathogenetic mechanisms to development of new biomarkers and drug discovery.

Inborn errors of metabolism (IEMs) are a group of Mendelian disorders resulting from genetic disruption of single metabolic enzymes. A large number of these reactions occurs in the liver. The study of these disorders has been instrumental to understanding the physiological consequences of metabolic reactions and pathogenesis of more common multifactorial diseases. In contrast to Mendelian diseases, which are due to severe impairment of single-enzyme reactions, common multifactorial diseases may result from mild impairment of several metabolic reactions (Lanpher et al., 2006). Nevertheless, our understanding of the consequences of single-enzyme deficiencies on metabolism as a whole are underappreciated, since most studies have been narrowly focused on the affected metabolic reactions, thus neglecting alterations of more distant metabolites. In most patients affected with IEMs, there are few therapeutic options that are often limited to common sense interventions aimed at either reducing the substrate or increasing the product of the affected reaction.

Tissue-specific genome-scale metabolic models, which have only recently become available through the efforts of the modeling community, allow in silico prediction of the effects of genetic or chemical perturbations on human metabolism (Gille et al., 2010; Jerby et al., 2010; Shlomi et al., 2009; Thiele et al., 2013). These computational models have been used to predict, for example, cancer drug targets (Folger et al., 2011), anti-aging drugs (Yizhak et al., 2014), and biomarkers for rare metabolic disorders (Duarte et al., 2007; Shlomi et al., 2009; Thiele et al., 2013).

Here we applied a computational approach to predict and analyze the metabolic alterations occurring in hepatocytes lacking alanine:glyoxylate aminotransferase (AGT), a peroxisomal enzyme encoded by the *AGXT* gene and mutated in primary hyperoxaluria type 1 (PH1).

PH1 is an autosomal recessive disease that presents with hyperoxaluria, progressive renal involvement, and systemic deposition of calcium oxalate in multiple organs and tissues. Although the enzyme is only expressed in hepatocytes, lack of AGT results in excessive production of oxalate by the liver, leading to oxalate-induced damage in several tissues, particularly in kidneys. PH1 is a severe disease that results in high morbidity, pain, disability, poor quality of life, and early death if treated late or