Next-Generation Metabolomics™

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Next-Generation Metabolomics: Metabolic Effects of MDR1 Inhibition

Summary

Panome Bio's Next-Generation Metabolomics analysis of Mdr1a KO rats revealed substantial dysregulation of many core metabolic processes, including lipid and nucleotide metabolism. These metabolic changes should be considered when analyzing metabolic effects of therapeutics that interact with Mdr1a and other drug efflux transporters.

Multidrug resistant protein 1a (Mdr1a) is an efflux transporter of both exogenous (e.g., drugs) and endogenous compounds in multiple tissues, including the brain, GI, liver, and kidneys. Accordingly, activity of Mdr1a will influence drug efficacy and toxicity, as well as organismal metabolism. To date, however, little is known about the metabolic effects of Mdr1a inhibition, despite the fact that many therapies have direct interactions with Mdr1a. Here, Next-Generation Metabolomics was used to study the metabolic effects of Mdr1a knock out (KO) in rat liver and serum.

Metabolomics profiling resulted in the measurement of >5,000 metabolites in the serum and >3,000 metabolites in the liver. Analysis of the differences in metabolite levels between Mdr1a KO and wild type (WT) rats revealed broad metabolic dysregulation (Figure 1).

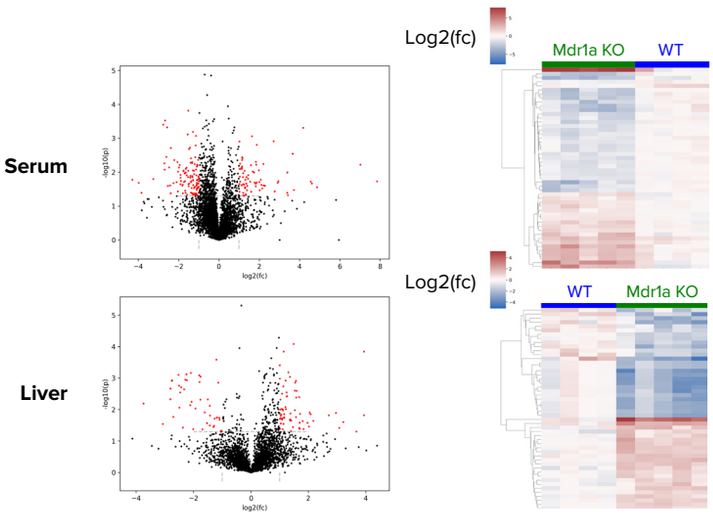

Figure 1: Dysregulated metabolomic profiles of Mdr1a KO serum and liver samples. Volcano plots showing the log2 fold changes and -log10 p-values of the metabolite levels in the serum (top) and liver (bottom) when comparing Mdr1a KO samples to WT. Red dots indicate statistically significant differences. The top 50 most significant metabolite alterations are shown in the heatmaps for both serum (top) and liver (bottom) samples.

In the serum, changes (both increases and decreases) in concentrations were seen for many glycerolipids and phospholipids (e.g., TAGs, DAGs). In the liver, dysregulated lipid metabolism was also observed. However, the changes primarily increased the levels of inositol lipids rather than glycerolipids. In addition to the lipid changes, multiple purine metabolism compounds had altered abundance in the serum and liver of KO rats, including hypoxanthine, xanthosine, and trimethyluric acid (only detected in serum), Figure 2. Uric acid and other purines are known substrates for Mdr1a. Interestingly, while xanthosine and trimethyluric acid (a derivative of uric acid) have lower abundance in KO rats, xanthosine (a nucleoside) has increased abundance in the serum and liver of KO rats. This suggests that Mdr1a has differential affinity for purines compared to nucleosides and resulted in metabolic compensation when purines are not effluxed. This rewiring of purine metabolism has major implications for downstream signaling and nucleotide production pathways.

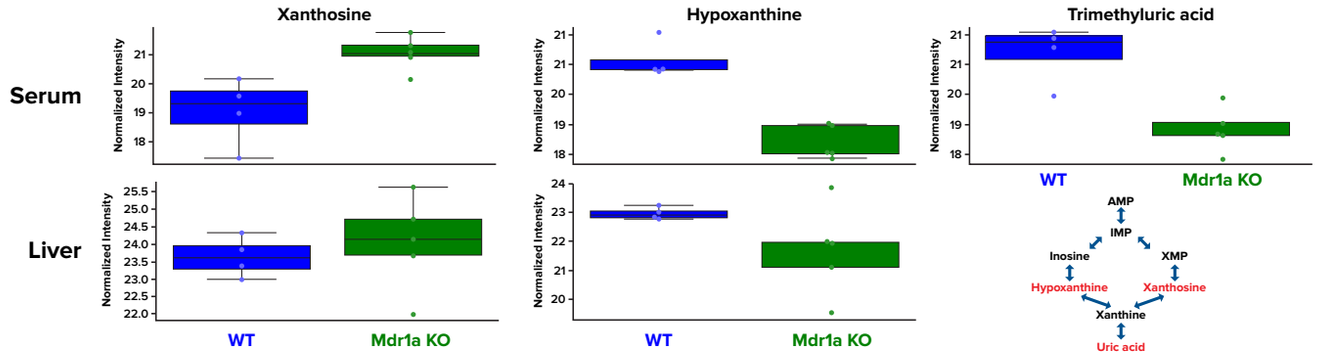

Figure 2: Dysregulated purine metabolism in Mdr1a KO rats. The levels of multiple purine metabolites were dysregulated in the serum of KO rats. These alterations were also present (to a lesser degree) in the livers of KO rats. Uric acid and other purines are known substrates of Mdr1a.

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