

4th International Conference and Exhibition on

Metabolomics & Systems Biology

April 27-29, 2015 Philadelphia, USA



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Metabolomics study of ketosis-associated increases in FGF21 in wild-type and PPAR alpha knockout mice

Fibroblast Growth Factor 21 (FGF21) is a novel endocrine hormone that has a range of beneficial metabolic effects and consequently a number of exogenously administered FGF21-based therapeutics is under investigation. A potential alternative therapeutic strategy would be to increase endogenous production of FGF21, however an improved understanding of the metabolic factors involved in the regulation of FGF21 production is required. The ketotic state is one of the best described physiologic stressors associated with elevated FGF21 production and this regulation occurs, at least in part, via PPAR alpha. Eli Lilly and Company's metabolomics platform, comprised of state-of-the-art instrumentation technologies, is capable of information delivery on hundreds of small molecules showing statistically significant biochemical alterations. Therefore, we applied a global metabolomics approach to examine the metabolic changes associated with FGF21 production in the livers of wild-type and PPAR alpha knockout mice in response to fasting or a ketogenic diet. Plasma FGF21 concentrations were increased by fasting and ketogenic diet in wild-type mice, but only by ketogenic diet in PPAR alpha KO mice and all increases correlated with increased FGF21 expression specifically in the liver. Correlation analysis of metabolomics data detected a strong link between hepatic FGF21 expression and the glutathione-mercapturic acid pathway. The curve clustering analysis identified 2-dehydro-D-gluconate, deoxyribose-phosphate, and glycerol-3-phosphate as metabolites associated with FGF21 production independent of the regulation of PPAR alpha. The current metabolomics approach provides a novel means for furthering our understanding of the physiologic regulation of FGF21 production.

Biography

Vladimir Tolstikov, PhD, is a Scientist at Eli Lilly and Company. He received BS and MS in Organic Chemistry in 1977 from M.V. Lomonosov Institute of Fine Chemical Technology, in Moscow, Russia. He received PhD in Organic Chemistry in 1983 from the Institute of Chemical Means for Plant Protection, Moscow, Russia. He is a pioneer in HILIC separations development applied to Metabolomics. During his career he was working in leading research institutions in USA, Germany, Hungary and Russian Federation. He has joined Eli Lilly and Company in 2012. He is author, contributor and participant of 45 conferences, 5 book chapters, and 54 articles.

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