304d Knowledge-Based Integration of Metabolic and Genetic Information to Identify Targets of Fatty Acid Toxicity

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Cells respond to alterations in the environment by changing the levels and activities of proteins. Many metabolic disorders are mediated through alterations in the levels of serum FFA and TNF-&alpha. Due to a significant increase in the incidences of obesity-related disorders it has become essential to identify the correct cellular targets to manipulate in order to protect cells from the deleterious effects of FFAs and TNF-&alpha. Hepatocytes are the first cells which metabolize fatty acids. Excess FFA levels alter the glucose and lipid metabolism of hepatocytes and are associated with liver disorders such as non-alcoholic steatohepatitis (NASH). We studied the genetic and metabolic responses of human hepatoma cell line (HepG2 cells) to identify the mechanism of toxicity of fatty acids. Saturated fatty acid, palmitate, was found to be cytotoxic. Application of metabolic flux analysis (MFA) to identify the changes in metabolic response upon exposure to palmitate revealed increased flux through fatty acid oxidation and diacylglycerol, indicating involvement of reactive oxygen species and protein kinase C (PKC). Pharmaceutical inhibition of these pathways significantly reduced the cytotoxicity of palmitate. Application of cDNA microarrays to identify the genetic response to exposure of the fatty acid revealed significant alteration in the redox-related genes and also in the levels of genes related to ion channels. Inhibition of K-ATP ion channels significantly reduced the toxicity of the fatty acid. Therefore, through knowledge-based integration of metabolic and genetic information, we were able to identify the pathways altered by exposure to FFAs. Genetic and metabolic information can complement each other to identify multiple targets to control the cell's response to pathogenic insults.