REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Systems biology and biochemical investigations of (fat) metabolism

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Seminar Room

While fats are an important source of energy and are involved in many other physiological processes, altered fat metabolism has been shown to be involved in pathogenesis of many metabolic disorders. My research has dealt with two divergent roles of fat metabolism- cell death caused by exposure to elevated levels of saturated free fatty acid (sFFA), and the beneficial effects of ketone bodies (KBs)- a product of fatty acid oxidation.

Excess caloric and fat intake is associated with hepatic lipid accumulation (steatosis), which later develops into steatohepatitis- a condition of liver inflammation and cell death. I was among the first to show that saturated, but not unsaturated FFAs, were cytotoxic to human hepatoma cell line. TNF-a, an inflammatory cytokine, exacerbated the cell toxicity due to sFFA but had no effect in presence of other FFAs. Physiological analyses revealed the mode of cell death and that the cytotoxicity was mediated by increased reactive oxygen species (ROS) production. The species of ROS and its sources were identified. Metabolic flux analysis (MFA) was conducted to identify altered fluxes, which revealed reduced glutathione synthesis due to reduced uptake of cysteine. Microarray analyses and systems biology modeling identified the genes, pathways and gene networks that play important roles in the toxicity. This research also generated tools to integrate high throughput data from multiple sources.

Ketone bodies are the products of FFA oxidation and are a major source of energy during starvation. They can also complement energy from glucose in conditions where glucose uptake or metabolism is reduced. Our lab has synthesized an ester of 3-hydroxybutyrate (BHB) and 1,3 butanediol, which we call ketone ester (KE), which can increase blood ketone levels. A diet containing KE raised blood ketone to much greater levels than previously achieved. This was associated with reduced voluntary food intake, increased mitochondrial biogenesis and uncoupling proteins in brown fat, and improved insulin sensitivity in mice. These results demonstrate the utility of the KE as a dietary supplement for obesity and insulin resistance.