TITLE: Role of fructose and uric acid in obesity and insulin resistance

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RESEARCH PROJECT DESCRIPTION (brief overview of background, hypothesis, methods, role of medical student, funding and relevant publications -- SHOULD NOT EXCEED ~ 250 WORDS)

Obesity and type 2 diabetes have been linked with the increase in consumption of added fructose-containing sugars. Fructose is distinct from other sugars in its initial metabolism via ketohexokinase (KHK), which bypasses regulated steps of glycolysis and rapidly depletes ATP followed by purine degradation via xanthine oxidoreductase (XOR) and, in addition, formation of the triglyceride precursors. The goal of our current project is to investigate mechanisms by which purine degradation via XOR during fructose metabolism by KHK contribute to metabolic syndrome. The initial hypothesis of this project is that purine degradation via XOR during fructose overload facilitates lipogenesis and low-grade inflammation, as well as oxidative and endoplasmic reticulum (ER) stresses, and represents an important prodiabetic mechanism. So far, we showed both KHK and XOR are critical for the lipogenesis and ectopic lipid deposition in the liver and kidney as well as proinflammatory changes including proinflammatory imbalance in the endocrine activity of the adipose tissue in response to fructose. XOR and KHK in human renal tubular cells and hepatocytes will be silenced with shRNA. KHK-knockout mice will be used in vivo followed by analysis of regulatory steps of lipogenesis. Currently we are investigating how purine degradation via XOR triggers ER-stress signaling, which mediate the prodiabetic effects of KHK-dependent purine degradation including lipogenesis, ectopic lipid deposition and inflammation. This work will provide mechanistic insights as well potential therapeutic approaches for the prevention and treatment of the metabolic syndrome.

This is a **basic research** attempting to answer important clinical questions.

Some publications (MSRP and other students are indicated with a **bold font)** :

1. Cirillo P, Gersch MS., **Scherer PM**., Kim KM, Gesualdo L, Henderson GN., Johnson RJ, *Sautin YY***.** Ketohexokinase-dependent Proinflammatory Effect of Fructose in Human Proximal Tubular Cells (2009) *J Am Soc Nephrol.*20: 545-53
2. **Baldwin, W**., S. **McRae, G. Marek, D. Wymer, V. Pannu**, Baylis C., Johnson R. J., and *Sautin Y. Y***.** (2011) Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. *Diabetes* (2011) 60(4):1258-69.

3. Ishimoto T, Lanaspa MA, Le MT, Garcia GE, Diggle CP, Maclean PS, Jackman MR, Asipu A, Roncal-Jimenez CA, Kosugi T, Rivard CJ, Maruyama S, Rodriguez-Iturbe B, Sánchez-Lozada LG, Bonthron DT, *Johnson RJ, Sautin YY*. Opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. *Proc Natl Acad Sci U S A*. 2012 109(11):4320-5.

4. **Marek G**, **Pannu V, Shanmugham P, Pancione B, Mascia D**, Crosson S, Ishimoto T**,** Sautin YY. Adiponectin resistance and proinflammatory changes in the visceral adipose tissue induced by fructose consumption via ketohexokinase-dependent pathway. *Diabetes*. 2015 Feb;64(2):508-18.