

Summer Research Program 2022 – Projects

Project #1

Title: Hexokinase-2 linked glycolytic overload and unscheduled glycolysis - driver of insulin resistance and development of type 2 diabetes

Description: Insulin resistance is the key metabolic driver of type 2 diabetes (T2D) development. It is present years before diabetes develops and is most marked in skeletal muscle. We need to correct insulin resistance to prevent and decrease the prevalence of T2D in Qatar. We recently proposed “*hexokinase-2 (HK2) linked glycolytic overload and unscheduled glycolysis*” as the initiating mechanism of insulin resistance. This is supported by experimental and clinical evidence and opens new routes to therapy and prevention of T2D. HK2-linked glycolytic overload and unscheduled glycolysis may be visualized by the study of HK2 protein increase and detachment from mitochondria in muscle cells incubated in high glucose concentration.

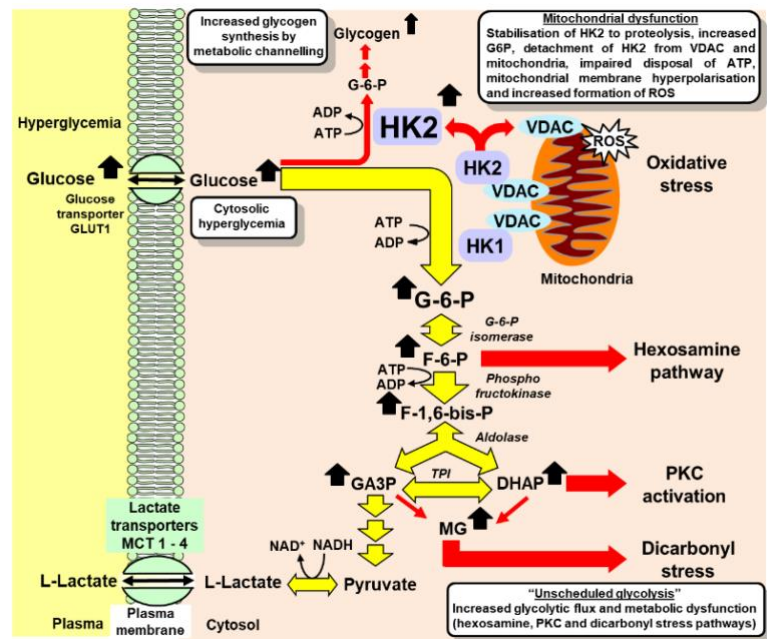
In this project we will culture murine C2C12 myoblasts and myotubes in low and high glucose concentration and study the accumulation of HK2 protein and detaching from mitochondria in muscle cells incubated in model hyperglycemia.

Techniques used: cell culture, Western blotting and immunohistochemistry.

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Figure 1. Glycolytic overload and unscheduled glycolysis in hyperglycemia. Key: red arrows - dysfunctional metabolism in unscheduled glycolysis. Metabolic intermediates in glycolysis from GA3P to pyruvate have been omitted for clarity. Abbreviations: DHAP, dihydroxyacetone phosphate; F-6-P, fructose-6-phosphate; F-1,6-bis-P, fructose-1,6-bisphosphate; G-6-P, glucose-6-phosphate; GA3P, glyceraldehyde-3-phosphate; HK1, hexokinase-1; HK2, hexokinase-2; MCT 1 – 4, monocarboxylate transporters 1 – 4; MG, methylglyoxal; ROS, reactive oxygen species; VDAC, voltage-dependent anion channel.



Reference: Rabbani, N., Xue, M. and Thornalley, P.J. (2022) Hexokinase-2-linked glycolytic overload and unscheduled glycolysis – driver of insulin resistance and development of vascular complications of diabetes. *Internat J. Molec. Sci.* 23, 2165.