Institut NeuroMyoGène CNRS UMR 5310 / INSERM U1217

Domaine Scientifique de la Doua - 16 rue Dubois, Bâtiment G. Mendel - 69622 Villeurbanne Cedex
Tel : (33) 0472431325 – Fax : (33) 0472432685 – www.inmg.fr

LES SÉMINAIRES DE L'INMG

Key signaling players in the control of hepatic gluconeogenesis

AMPK or other AMPK-related/AMP-regulated enzymes ?

Par

Kei Sakamoto

(Invité par Rémi MOUNIER)

Nestlé Institute of Health Sciences SA
EPFL Innovation Park, bâtiment G
1015 Lausanne (Switzerland)
http://www.nestleinstitutehealthsciences.com

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Salle FONTANNES
Bât. Darwin D - RdC
1, rue Raphaël DUBOIS
69100 Villeurbanne - Domaine Universitaire de La Doua

Abstract

Hepatic glucose production is a key physiologic process that ensures energy balance for glucose-dependent organs/cells such as brain. The inability of insulin to suppress hepatic glucose output is a major aetiological factor in the hyperglycaemia of type 2 diabetes.
LKB1, originally identified as a tumor suppressor protein, is currently thought as a critical regulator of cellular metabolism and growth by controlling the activity of AMP-activated protein kinase (AMPK) and also 12 other kinases that are closely related to AMPK. Among those AMPK-related kinases, we have recently identified that Salt-Inducible Kinase (SIK) plays an important role as a gluconeogenic gatekeeper in the liver.

Metformin exerts its major effect via inhibition of hepatic glucose production. This is thought to be mediated through decreased hepatic energy charge (i.e. increasing AMP/ATP ratio) via inhibition of mitochondrial respiration. The long-standing belief that 5'-adenosine monophosphate (AMP)-activated protein kinase (AMPK) mediates the anti-hyperglycaemic action of metformin has recently been challenged in experiments using mice lacking hepatic AMPK. I will discuss our recent data demonstrating AMP-mediated allosteric inhibition of an enzyme involved in gluconeogenesis plays a key role in acute glucose-lowering effect of metformin.

Recent Publications

Ducommun, S., Deak, M., Sumpton, D., Ford, R.J., Núñez Galindo, A., Kussmann, M., Viollet, B., Steinberg, G.R., Foretz, M., Dayon, L., Morrice, N.A., Sakamoto, K. (2015) Motif affinity and mass spectrometry proteomic approach for the discovery of cellular AMPK targets: Identification of mitochondrial fission factor as a new AMPK substrate. Cell Signal. 7:978-88.

Patel, K., Foretz, M., Marion, A., Campbell1, D.G., Gourlay, R., Boudaba, N., Tournier, E., Titchenell, P., Peggie, M., Deak, M., Wan, M., Kaestner, K.H., Göransson, O., Viollet, B., Gray, N.S., Birnbaum, M.J., Sutherland, C., Sakamoto, K. (2014) The LKB1-Salt-inducible kinase pathway functions as a key gluconeogenic suppressor in the liver. Nat Commun. 5:4535.

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