Novel mechanisms of metabolic sensing by CaMKK2

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The Ca^{2+}-calmodulin dependent protein kinase kinase-2 (CaMKK2) is a core mediator of Ca^{2+}-signal transduction in cells, and a key regulator of whole-body energy metabolism. Inhibition of CaMKK2 protects against high-fat diet induced obesity, glucose intolerance and insulin resistance (1,2), however the molecular mechanisms that link CaMKK2 to cellular energy metabolism are unknown. Here we show that CaMKK2 is directly activated by long chain fatty acyl-CoA (LCFA-CoA) metabolites and □-ketoglutarate, two major intermediates of lipid and energy metabolism, respectively. CaMKK2 activation by LCFA-CoA is dependent on a novel motif comprised of a glycine tetrad and tandem proline residues (G4-P2P motif) located within the C-terminus of CaMKK2. On the other hand, binding of □-ketoglutarate activates CaMKK2 by stimulating phosphorylation of an activating site (Ser88) in the N-terminal sequence of CaMKK2. These two novel modes of activation provide distinct mechanisms for directly coupling CaMKK2 to fuel and energy metabolism and reveals a new role for CaMKK2 as a metabolic sensor.

1. Anderson, K. A., Lin, F., Ribar, T. J., Stevens, R. D., Muehlbauer, M. J., Newgard, C. B., and Means, A. R. (2012) Deletion of CaMKK2 from the liver lowers blood glucose and improves whole-body glucose tolerance in the mouse. *Mol Endocrinol* **26**, 281-291
2. Anderson, K. A., Ribar, T. J., Lin, F., Noeldner, P. K., Green, M. F., Muehlbauer, M. J., Witters, L. A., Kemp, B. E., and Means, A. R. (2008) Hypothalamic CaMKK2 contributes to the regulation of energy balance. *Cell Metab* **7**, 377-388