

Makoto Funaki, M.D., Ph.D.



Contact address

Department of Physiology
Institute for Medicine & Engineering
University of Pennsylvania
1142 Vagelos, 3340 Smith Walk
Philadelphia, PA, 19104-6383
Phone: (215) 573-5307
Fax: (215) 573-6815
Email: funaki@mail.med.upenn.edu

Education

1991 M.D. University of Tokyo, School of Medicine
1997 Ph.D. University of Tokyo, Graduate School of Medicine

Professional Positions

1991-1992 Residency, University of Tokyo Hospital
1992-1993 Residency, Tokyo Postal Service Agency Hospital
1997-2000 Senior Researcher, The Institute for Adult Disease, Asahi Life Foundation
2000-2001 Post Doctoral Researcher, University of Pennsylvania
2002-2006 Research Associate, University of Pennsylvania
2005-present Adjunct Faculty, University of Tokushima
2006-present Research Assistant Professor, University of Pennsylvania

Awards & Honors

1999 Research Award from Japan Insulin Study Group
2005 American Diabetes Association Junior Faculty Award

Research Area

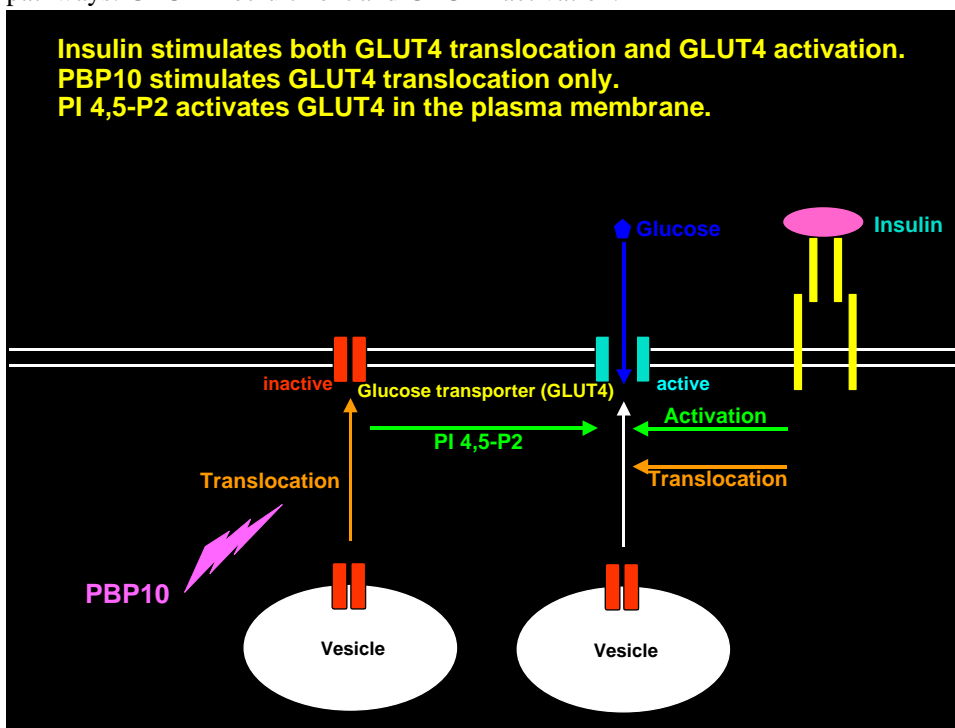
Signal transduction leading to GLUT4-mediated glucose uptake

The insulin-stimulated glucose uptake into skeletal/cardiac muscles and adipose tissues through the insulin-regulated glucose transporter (GLUT4) plays a pivotal role in maintaining a normal blood glucose level. In fact, reduced glucose uptake into these tissues in response to insulin, a condition called 'insulin resistance', is associated with the pathophysiology of type 2 diabetes. Thus, revealing the signal transduction pathway from insulin stimulation to glucose uptake through GLUT4 is crucial to diabetes research.

In the absence of insulin, GLUT4 is stored in intracellular vesicles. In response to acute insulin stimulation, these vesicles translocate to the plasma membrane resulting in the redistribution of GLUT4 in the plasma membrane, where GLUT4 can facilitate glucose uptake.

Recently, we have reported that, by applying a cell-permeable phosphoinositide-binding

peptide (PBP10), GLUT4 successfully translocated to the plasma membrane to face the extracellular surface of the cells, but did not transport glucose at all. Thus, GLUT4 translocation to the plasma membrane is necessary but not sufficient for insulin-stimulated glucose uptake. GLUT4 needs to be activated at the plasma membrane, demonstrating the separation of insulin signaling into two distinctive pathways: GLUT4 recruitment and GLUT4 activation.



Phosphoinositide metabolism and the cytoskeleton have been shown to be involved in insulin-stimulated glucose uptake. In our recent report, we found that PBP10, by its ability to bind to PI 4,5-P2, sequesters PI 4,5-P2 from its binding partners. Replenishing PI 4,5-P2 after PBP10 treatment successfully activated GLUT4 that had translocated to the plasma membrane by PBP10. Thus, PI 4,5-P2 in the plasma membrane, presumably through F-actin remodeling, has an ability to activate GLUT4 in the plasma membrane. Now we are working on the role of phosphoinositide metabolism and the cytoskeleton in GLUT4 translocation and GLUT4 activation, respectively, by utilizing biochemical, biophysical and a state-of-the-art 3-D imaging technique.

These studies will help to identify new therapeutic targets against insulin resistance.

Selected Publications

1. Inukai K, **Funaki M**, Ogihara T, Katagiri H, Kanda A, Anai M, Fukushima Y, Hosaka T, Suzuki M, Shin BC, Takata K, Yazaki Y, Kikuchi M, Oka Y, Asano T; p85alpha gene generates three isoforms of regulatory subunit for phosphatidylinositol 3-kinase (PI 3-Kinase), p50alpha, p55alpha, and p85alpha, with different PI 3-kinase activity elevating responses to insulin. *J Biol Chem.* 1997 Mar 21; 272(12): 7873-82.
2. **Funaki M**, Katagiri H, Kanda A, Anai M, Nawano M, Ogihara T, Inukai K, Fukushima Y, Ono H, Yazaki Y, Kikuchi M, Oka Y, Asano T; p85/p110-type phosphatidylinositol kinase phosphorylates not only the D-3, but also the D-4 position of the inositol ring. *J Biol Chem.* 1999 Jul 30; 274(31): 22019-24.
3. Inukai K, **Funaki M**, Nawano M, Katagiri H, Ogihara T, Anai M, Onishi Y, Sakoda H, Ono H, Fukushima Y, Kikuchi M, Oka Y, Asano T; The N-terminal 34 residues of the 55 kDa regulatory

- subunits of phosphoinositide 3-kinase interact with tubulin. *Biochem J.* 2000 Mar 1; 346(Pt 2): 483-489.
4. Asano T, Kanda A, Katagiri H, Nawano M, Ogihara T, Inukai K, Anai M, Fukushima Y, Yazaki Y, Kikuchi M, Hooshmand-Rad R, Heldin CH, Oka Y, **Funaki M**; p110beta is Up-regulated during differentiation of 3T3-L1 cells and contributes to the highly insulin-responsive glucose transport activity. *J Biol Chem.* 2000 Jun 9; 275(23): 17671-6
 5. Inukai K, **Funaki M**, Anai M, Ogihara T, Katagiri H, Fukushima Y, Sakoda H, Onishi Y, Ono H, Fujishiro M, Abe M, Oka Y, Kikuchi M, Asano T; Five isoforms of the phosphatidylinositol 3-kinase regulatory subunit exhibit different associations with receptor tyrosine kinases and their tyrosine phosphorylations. *FEBS Lett.* 2001 Feb 9; 490(1-2): 32-8.
 6. Wada T, Sasaoka T, **Funaki M**, Hori H, Murakami S, Ishiki M, Haruta T, Asano T, Ogawa W, Ishihara H, Kobayashi M; Overexpression of SH2-Containing Inositol Phosphatase 2 (SHIP2) Results in Negative Regulation of Insulin-Induced Metabolic Actions in 3T3-L1 Adipocytes via its 5'-Phosphatase Catalytic Activity. *Mol Cell Biol.* 2001 Mar; 21(5): 1633-46.
 7. Cunningham CC, Vegners R, Bucki R, **Funaki M**, Korde N, Hartwig JH, Stossel TP, Janmey PA; Cell permeant polyphosphoinositide-binding peptides that block cell motility and actin assembly. *J Biol Chem.* 2001 Nov 16; 276(46): 43390-9.
 8. Onishi-Haraikawa Y, **Funaki M**, Gotoh N, Shibuya M, Inukai K, Katagiri H, Fukushima Y, Anai M, Ogihara T, Sakoda H, Ono H, Kikuchi M, Oka Y, Asano T; Unique phosphorylation mechanism of Gab1 using PI 3-kinase as an adaptor protein. *Biochem Biophys Res Commun.* 2001 Oct 26; 288(2): 476-82.
 9. **Funaki M**, Randhawa P, Janmey P; Separation of Insulin Signaling into Distinct GLUT4 Translocation & Activation Steps. *Mol Cell Biol.* 2004 Sep; 24(17): 7567-77.
 10. Yeung T, Georges PC, Flanagan L, Marg B, Ortiz M, **Funaki M**, Zahir N, Ming M, Weaver V, Janmey PA; Effects of substrate stiffness on cell morphology, cytoskeletal structure, and adhesion. *Cell Motility and the Cytoskeleton*, 2004 Nov 30;60(1):24-34
 11. Sasaoka T, Fukui K, Wada T, Murakami S, Kawahara J, Ishihara H, **Funaki M**, Asano T, Kobayashi M; Inhibition of endogenous SHIP2 ameliorates insulin resistance caused by chronic insulin treatment in 3T3-L1 adipocytes. *Diabetologia.* 2005 Jan 15 ;48(2):336-44
 12. **Funaki M**, DiFransico L, Janmey PA.; PI 4,5-P2 stimulates glucose transport activity of GLUT4 in the plasma membrane of 3T3-L1 adipocytes. *Biochim Biophys Acta.* 2006 Aug;1763(8):889-99. Epub 2006 May 24.