Homeodomain interacting protein kinase 2 is downregulated through the peroxisome proliferator-activated receptor gamma signaling pathway in an insulin-resistant population

Homeodomain interacting protein kinase 2 (HIPK2), the highly conserved nuclear serine/threonine kinase, is known to act as a co-repressor through interacting with a number of transcription factors. Notably, HIPK2 inhibits cell growth through the activation of p53. However, its in vivo function in insulin resistance is still unknown.

Recently, the discovery by Sjolund et al. has implicated HIPK2 as a central modulator of adipogenesis. They found that deletion of HIPK2 in mice gave rise to decreased adipogenesis and increased insulin-sensitivity independence of the peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway. According to their result, we hypothesize that the expression of HIPK2 in the insulin-resistant population might be upregulated.

To testify our supposition, we analyzed the publicly available expression data from two human insulin-resistant expression data in GEO datasets that use the same platform. Contrary to our deduction, the HIPK2 gene was downregulated in the insulin-resistant population (Figure 1a,b).

PPARγ is the key transcription factor in adipogenesis, as well as glucose and fatty acid metabolism, and alterations in the pathway lead to insulin resistance and type 2 diabetes mellitus. According to the report by Sjolund et al., the function of HIPK2 was not mediated by a PPARγ-dependent mechanism. However, we identified that some downstream targets of PPARγ, which Sjolund et al. mentioned, were downregulated in adipocytes in insulin-resistant people, which is synchronously expressed with HIPK2 messenger ribonucleic acid expression (Figure 1c). Some transcription cofactors of PPARγ shown by GeneMANIA (http://www.genemania.org/) were also downregulated in the adipocytes of the insulin-resistant population (Figure 1d).

Rosiglitazone (Rosi), a member of the thiazolidinediones and an agonist of PPARγ, works as an insulin sensitizer in type 2 diabetes mellitus. The present results showed that HIPK2 messenger ribonucleic acid expression was significantly increased in the presence of both Rosi and overexpressed PPARγ in murine marrow-derived U-33 cells, indicating a tendency of increased HIPK2 expression after administration of insulin sensitizer (Figure 1e). In agreement with this, several other articles published the same results that HIPK2 expression was elevated after administration of insulin sensitizer, rosiglitazone and troglitazone (Table S1), suggested by The Comparative Toxicogenomics Database (http://ctd-base.org/).

Taken together, despite of Sjolund et al. discovery that HIPK2 deletion in mice induces increased insulin sensitivity and was not mediated by the PPARγ pathway, our data suggest that downexpression of HIPK2 was discovered in a population that suffered from decreased insulin sensitivity (insulin resistance) through the PPARγ-dependent pathway. This discrepancy might be caused by the following reasons: (i) metabolic differences between humans and murine; (ii) the discovery by Sjolund et al. was carried out on skeletal muscle, where the present results were shown in adipocytes; and (iii) our discovery was the result of a subset of humans, accordingly, the discovery by Sjolund et al. was based on a few HIPK2 knockout mice, the two studies all await further verification. Furthermore, we also showed that administration of insulin sensitizer could promote the elevated expression of HIPK2, thus providing a benefit for treatment of insulin resistance.

*Corresponding author. Jie Qiao
Tel.: +86-10-8226-6836
Fax: +86-10-8226-6849
E-mail address: jie.qiao@263.net
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Figure 1 | Decreased expression of homeodomain interacting protein kinase 2 (HIPK2) in an insulin resistant population was associated with the peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway. (a,b) Expression of HIPK2 detected by gene expression microarray in panels of an insulin-resistant population using adipocytes (***P < 0.001) compared with the corresponding control cells, as examined by unpaired two-sided Student’s t-test. (c) The messenger ribonucleic acid (mRNA) levels of PPARγ, CCAAT/enhancer-binding protein alpha (CEBPA), CCAAT/enhancer-binding protein beta (CEBPB), fatty acid-binding protein 4 (FABP4), mesoderm specific transcript (MEST), cell death-inducing dFFA-like effector a (CIDEA), peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PPARGC1A) and uncoupling protein 1 (UCP1) in adipocytes of an insulin-resistant population (IR) in two GSE datasets (*P < 0.05, **P < 0.01 and ***P < 0.001) compared with the corresponding controls (insulin sensitive [IS]). (d) The mRNA levels of PPARα, PPARδ, retinoid X receptor alpha (RXRA), fatty acid binding protein 1 (FABP1), nuclear receptor coactivator 4 (NCOA4), transducin (beta)-like 1X-linked (TBL1X) in the adipocytes of an insulin-resistant population in two GSE datasets (*P < 0.05, **P < 0.01 and ***P < 0.001) compared with the corresponding controls. (e) The mRNA expression of HIPK2 in the presence of rosiglitazone (Rosi) or/and overexpressed PPARγ, detection was carried out 24 h after administration of Rosi with two replicates. Statistical significance was determined by paired two-tailed Student’s t-test (*P < 0.05). Data are presented as mean ± standard error of the mean, and was extracted from the Gene Expression Omnibus data repository (accession number: GSE13070, GSE20950 and GSE10192). DMSO, dimethylsulfoxide.
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DISCLOSURE
The authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional Supporting Information may be found in the online version of this article:
Table S1 | Insulin sensitizer induced homeodomain interacting protein kinase 2 (HIPK2) messenger ribonucleic acid expression.