JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

# Cell-autonomous defects contribute to insulin resistance in skeletal muscle

Insulin resistance is a major factor in the development of type2 diabetes. Skeletal muscle is the first organ to insulin resistance, which precedes onset of type2 diabetes and be predictive of the disease[1]. Despite the fact that skeletal muscle insulin resistance is clearly involved in the pathogenesis of type2 diabetes, it has been unclear whether the underlying mechanism crucially involves defects in cell-autonomous signaling or alterations in blood lipids, hormones and other systemic changes that modulate insulin action in type2 diabetes.

Batista *et al.*[2] recently modeled cell-autonomous skeletal muscle insulin resistance using myoblasts (iMyos) differentiated from induced pluripotent stem cells (iPSC) of type2 diabetes patients to avoid interference by systemic factors. They derived iPSC lines from eight healthy controls and eight type2 diabetes , equally divided between and and matched by age. The donor cohort of type2 diabetes comprised mostly middle-aged people of European descent higher body mass index and chronic hyperglycemia.

In the study, first compared the insulin signaling, glucose uptake and cellular respiration in iMyos between the two groups. They found that compared iMyos from controls, type2 diabetes iMyos had significantly lower insulin-induced phosphorylation of protein kinaseB$^{T308}$, glycogen synthase kinase-3$\alpha^{S21}$/-3$\beta^{S9}$ and forkhead box proteinO1$^{T24}$/O3a$^{T32}$, which strongly suggests cell-autonomous impairment of insulin signaling. In addition, glucose uptake and mitochondrial and non-mitochondrial respiration were impaired in type2 diabetes iMyos, mimicking the changes observed *invivo* in muscle of patients in previous studies[3,4] (Table 1).

They further global phosphoproteomic analysis and network analysis of the proteins involved in signal transduction to provide a detailed, multifaceted examination of the pathogenesis of insulin resistance occurring autonomously in skeletal muscle of type2 diabetes patients. By global phosphoproteomic analysis of 16 samples in the insulin-acting cluster, 125 phosphosites were found to be increased by insulin stimulation. The sites of phosphorylation included many proteins known to be involved in insulin receptor signaling as well as a number of newly identified phosphorylation events. In type2 diabetes, it affected specific phosphorylation events in both the proximal (insulin receptor substrate-1, -2) and downstream , mammalian target of rapamycin portions of the insulin signaling pathway rather than causing disruption of the entire insulin action network (Table 1) In addition, they identified several phosphosites on proteins involved in insulin signaling in type2 diabetes iMyos that are dysregulated in the basal state independent of insulin action. They further analyzed the entire phosphoproteome and found that in addition to changes in basal protein phosphorylation of proteins in the normal insulin signaling pathway, there were numerous changes in basal protein phosphorylation of type2 diabetes iMyos in other regulatory pathways. In both the basal and insulin-stimulated states, type2 diabetes was found to be characterized by a broad network of signaling changes, which included proteins involved in regulation of ribonucleic acid processing, gene expression, cytoskeletal remodeling and vesicular trafficking (Table 1).

On the basis of these findings, Batista *et al.*[2] propose an integrative signaling map of the two major components of the altered phosphoproteome of type2 diabetes iMyos: (i) failure of the insulin-signaling downstream of -1, and pathways and (ii) disruption of a broader network of basal phosphorylation. The defects in the insulin signaling cascade are deeply integrated with the alterations in basal phosphorylation of transcriptional regulators, splicing factors, chromatin remodeling, vesicular transport, and cytoskeletal remodeling and cytoskeletal components observed in type2 diabetes iMyos. The mechanisms they uncovered that are impaired in skeletal muscle of type2 diabetes iMyos are summarized in Table 1. Their

**Table 1** | Major pathogenesis and signaling underlying cell-autonomous muscle insulin resistance in type2 diabetes

| Analysis | Findings |
|---|---|
| Metabolic features | • ↓Insulin signaling<br>• ↓Glucose uptake<br>• ↓Mitochondrial respiration |
| Global phosphoproteomics/ network analysis | Insulin signaling<br>• Disruption of IRS/AKT/mTOR pathway<br>Basal phosphorylation independent of insulin signaling<br>• Gene transcription<br>• mRNA splicing<br>• Chromatin remodeling<br>• Vesicular transport<br>• Cytoskeletal remodeling |

AKT, protein kinaseB; IRS, insulin receptor substrate; mRNA, messenger ribonucleic acid; mTOR, mammalian target of rapamycin.

*Corresponding author. Nobuya Inagaki
Tel.: +81-75-751-3560
Fax: +81-75-751-4244
E-mail address: inagaki@kuhp.kyoto-u.ac.jp
Received 25 March 2021; revised 1 April 2021; accepted 5 April 2021

findings, in addition to being consistent with those obtained from previous skeletal muscle biopsies[4], a novel network of skeletal muscle signaling abnormalities underlying type2 diabetes.

The novel approach using global phosphoproteomics and integrated phosphorylation network analysis has revealed insights that could not be elucidated using existing methods. Their findings are of great interest as they a new, previously unrecognized layer of cell-autonomous defects underlying insulin resistance in skeletal muscle and open up opportunities for the development of new therapeutic approaches to type2 diabetes. Furthermore, network analysis can provide understanding and insight this network that are a dramatic improvement on traditional analysis.

Future perspectives and the limitations, including those mentioned by the authors, are as follows. Eight iPSC-derived myoblasts in each diabetic and non-diabetic group were examined in the study. However, type2 diabetes is clinically and genetically very heterogeneous and it is impossible to represent all potential subgroups. In addition, the pathogenesis of type2 diabetes in East Asian patients might be different from that of the European patients enrolled as donors[5]. Future studies are required to clarify whether ethnic differences affect the pathology of cell-autonomous insulin resistance in skeletal muscle. The authors note that they derived their iPSC lines from primary myoblast cultures to maximize both the differentiation efficiency and the likelihood of capturing any cell-specific disease phenotype[1]. As iPSCs have universal differentiation capacity, determining whether or not the cell autonomy of signals related to insulin resistance differs among cell types in terms of organ specificity, for example, by differentiating the same iPSCs into hepatocytes or adipocytesother targets of insulin actionis required. Nevertheless, this seminal study using iPSCs delineates the autonomous mechanism of insulin resistance at the level of individual organ, and opens a novel path to understand this very important physiological mechanism as well as to treatment of type2 diabetes.

## DISCLOSURE

The authors declare no conflict of interest.

Yoshihito Fujita, Nobuya Inagaki*
*Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

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Doi: 10.1111/jdi.13557