Insulin resistance is a major factor in the development of type 2 diabetes. Skeletal muscle is the first organ to insulin resistance, which precedes onset of type 2 diabetes and be predictive of the disease. Despite the fact that skeletal muscle insulin resistance is clearly involved in the pathogenesis of type 2 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 type 2 diabetes.

Batista et al. recently modeled cell-autonomous skeletal muscle insulin resistance using myoblasts (iMyos) differentiated from induced pluripotent stem cells (iPSC) of type 2 diabetes patients to avoid interference by systemic factors. They derived iPSC lines from eight healthy controls and eight type 2 diabetes, equally divided between and and matched by age. The donor cohort of type 2 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, type 2 diabetes iMyos had significantly lower insulin-induced phosphorylation of protein kinase B (AKT), glycogen synthase kinase-3β (GSK3β), and forkhead box protein O1 (FOXO1). This suggested cell-autonomous impairment of insulin signaling. In addition, glucose uptake and mitochondrial and non-mitochondrial respiration were impaired in type 2 diabetes iMyos, mimicking the changes observed in vivo in muscle of patients in previous studies (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 type 2 diabetes patients. By global phosphoproteomic analysis of 16 samples in the insulin-acting cluster, 125 phosphorylations 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 type 2 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 type 2 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 type 2 diabetes iMyos in other regulatory pathways. In both the basal and insulin-stimulated states, type 2 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. propose an integrative signaling map of the two major components of the altered phosphoproteome of type 2 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 type 2 diabetes iMyos. The mechanisms they uncovered that are impaired in skeletal muscle of type 2 diabetes iMyos are summarized in Table 1.

Table 1 | Major pathogenesis and signaling underlying cell-autonomous muscle insulin resistance in type 2 diabetes

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

AKT, protein kinase B; IRS, insulin receptor substrate; mRNA, messenger ribonucleic acid; mTOR, mammalian target of rapamycin.
findings, in addition to being consistent with those obtained from previous skeletal muscle biopsies\textsuperscript{4}, a novel network of skeletal muscle signaling abnormalities underlying type 2 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 reveal 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 type 2 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, type 2 diabetes is clinically and genetically very heterogeneous and it is impossible to represent all potential subgroups. In addition, the pathogenesis of type 2 diabetes in East Asian patients might be different from that of the European patients enrolled as donors\textsuperscript{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\textsuperscript{3}. 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 adipocytes other targets of insulin action is 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 type 2 diabetes.

**DISCLOSURE**

The authors declare no conflict of interest.

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