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Extended Abstract

Project to establish a longitudinal cohort of Type 1 diabetes in China

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a complex multifactorial disease with a high prevalence in the world. Insulin resistance and impaired insulin secretion are the two major abnormalities in the pathogenesis of T2DM. Skeletal muscle is responsible for over 75% of the glucose uptake, thus plays a critical role in T2DM. Here, we attempted to provide a better understanding of abnormalities in this tissue. Cognitive impairment caused by diabetes has been gradually recognized. Generally, nicotinic acetylcholine receptors (nAChRs) play an important role in the pathogenesis in dementia disorders including Alzheimer's disease (AD). However, the expression of nAChRs in the brains of type 2 diabetes mellitus (T2DM) is unexplored. This study explored the alterations of nAChRs in the postmortem brains of patients with T2DM and brains of db/db mice. Morris water maze test was used to appraise the ability of spatial learning and memory; Western blotting and RT-qPCR were performed to determine the expressions of target protein and mRNA, respectively; TUNEL was used to detect the apoptosis of neurons. We found that the protein levels of nAChR α7 and α4 subunits were significantly decreased and the apoptosis rates in neurons elevated in the hippocampus of T2DM patients and db/db mice as comparison to controls.

T2DM is a complex multifactorial disorder. The main cause of T2DM is impaired insulin secretion by pancreatic β-cells, usually due to having a background of reduced sensitivity to insulin in target tissues. Skeletal muscle, liver, and adipose tissues are the key insulin-sensitive tissues in which skeletal muscle is responsible for over 75% of the glucose uptake, thus takes the major role in lowering the blood glucose level. Therefore, there is an essential need to improve our understanding of the molecular mechanisms underlying insulin resistance in skeletal muscle to develop better prognostic signatures and to identify molecular drivers that can be therapeutically targeted. However, considerable experimental and computational attempts have been made to determine the molecular mechanisms involved in insulin resistance, the exact underlying cause of it, is unclear and failure of current therapies in some cases has occurred. One possible reason for this failure could be the multifactorial nature of T2DM. It is probable to and different groups of molecular mechanisms that all lead to insulin resistance and apply precision therapy for each group. This approach possibly improves the success rate of T2DM treatment.

Methods: We have explored the muscle gene expression pattern in healthy and newly diagnosed T2DM individuals using supervised and unsupervised classification along with examining the potential of sub-typing based on the gene expression pattern in patients.

Results: A machine-learning technique applied to identify a pattern of gene expression that could potentially discriminate between normoglycemic and diabetic groups. A gene set comprises 26 genes identified, which was able to discriminate healthy from diabetic individuals with 94% accuracy after 10-fold stratified cross-validation. In addition, three distinct clusters with different dysregulated genes and metabolic pathways identified in diabetic patients.

Conclusion: This study implies that it seems the disease has triggered through different cellular/molecular mechanisms and it has the potential to be sub-typing. Possibly, subtyping of T2DM patients in combination with their real clinical profiles will provide a better understanding of abnormalities in each group and lead to the recommendation of the appropriate precision therapy for each subtype in the future.

KEYWORDS

Type 2 Diabetes, Subtype, Classification, Clustering, Flux variability analysis, Muscle, insulin resistance, Metabolic modeling

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