Letter To Editor

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Histone Deacetylases Inhibition on Diabetes Mellitus Control: A promising, but Long Way to go

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Diabetes mellitus (DM) is a chronic disease affecting 285 million individuals worldwide, and is estimated to increase by the year 2030 to 439 million patients [1]. The effective treatment in reducing DM risk is insufficient since the pathophysiology of DM cardiomyopathy is not well established. Emerging concepts have link epigenetic mechanisms in the regulation of DM and its cardiovascular complications, which are the leading causes of DM mortality or morbidities. Among them, histone deacetylases (HDACs) play a crucial role in the transcription of genes to modulate proliferation, migration and death of cells [2]. HDACs are enzymes that compete with histone acetyltransferase to regulate the acetylation of lysine residues during chromatin remodeling [3]. Recent studies indicate that targeting HDACs is a promising therapeutic strategy for a number of other diseases such as DM, as demonstrated in cellular and animal models [4-7], and DM complications [8-11].

We recently evaluated the effect of HDAC inhibitor, MPT0E01, in a streptozotocin-nicotinamide induced DM rat cardiomyocytes, and found that this pan-HDAC inhibitor significantly attenuated DM cardiomyopathy through modulation of cardiac peroxisome proliferator-activated receptors (PPARs), fatty acid metabolism, and proinflammatory cytokines [12]. Similarly, MPT0E014 was shown to suppress cardiac fibrosis [13], and modulate cardiac PPARs, and inflammatory cytokines in a heart failure [14]. The effect of MPT0E014 on cardiac PPARs may have resulted from its anti-inflammatory activity. Besides, MPT0E014 may modulate cardiac metabolism through its effects on PPARs and inflammatory cytokines to diminish the accumulation of fatty acids in DM hearts.

Although laboratory evidences support the potential role of HDAC inhibition on DM and its complications, the precise mechanisms underlying the effects of HDAC inhibitors are not clear. Several possibilities at least are expected to involve the effects of HDAC inhibition on DM control, which includes glucose homeostasis, inflammation and oxidative stress, fatty acid metabolisms, and mitochondria regulation (Figure 1).

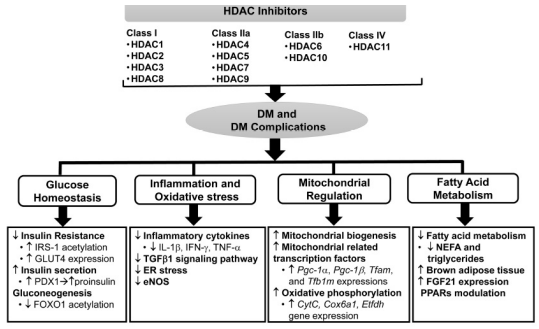

Figure 1

Figure 1: Effect of histone deacetylases (HDACs) inhibitors on diabetes mellitus (DM). Diagram summarized the mechanisms by which inhibition of HDACs regulate DM and its complications.

Abbreviations

IRS-1: Insulin receptor substrate-1; GLUT: Glucose transporter type 4; PDX: Pancreatic and duodenal homeobox 1; FOXO: Forkhead box protein O1; IL-1β: Interleukin-1β; IFN-γ: Interferon gamma; TFN-α: Tumor necrosis factor-α; TGFβ: Transforming growth factor beta 1; ER: Endoplasmic reticulum; eNOS: Endothelial nitric oxide synthase; *Pgc-1α*: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; *Pgc-1β*: Peroxisome proliferator-activated receptor gamma coactivator 1-beta; *Tfam*: Mitochondrial transcription factor A; *Tfb1m*: Transcription factor B1 mitochondrial; *Cytc*: Cytochrome

complex; *Cox6a:* Cytochrome c oxidase 6a1; *Etfdh*: Electron transferring flavoprotein dehydrogenase; NEFA: Non-esterified fatty acid; FGF: Fibroblast growth factor 21; PPARs: Peroxisome proliferator-activated receptors.

In addition, the individualized classes of HDAC inhibition responsible for their distinctive role in DM control are not elucidated. It is not clear whether MPT0E014 has direct effects on DM cardiac metabolism by directly measuring carbohydrate and fatty acid utilization. In addition, the downstream signaling pathways underlying the activity of MPT0E014 on myocardial inflammatory cytokines and PPAR expressions, the direct impact of MPT0E014 on PPAR gene expressions, and the effects of MPT0E014 on the regulation of myocardial autophagy need further investigations. It is mandatory to study the effects of HDAC inhibition in more clinically relevant type 2 DM model (not from streptozotocin-induction) and evaluate their effects in other organs related to glucose homeostasis such as pancreas, liver, muscles and adipose tissues.

In conclusion, the HDAC inhibition is a promising strategy in controlling DM and its complications. But it still has a long way to go due to several curious questions remaining unsolved.

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