Therapeutic silencing of centromere protein X ameliorates hyperglycemia in zebra fish and mouse models of type 2 diabetes mellitus

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Type 2 diabetes mellitus (T2DM) is characterized by persistent hyperglycemia, an d contributed by genetic and environmental factors. Optimum T2DM management involves early diagnosis and effective glucose-lowering therapies. Further research is warranted to improve our understanding of T2DM pathophysiology and reveal potential roles of genetic predisposition. We have previously developed an obesity- induced diabetic zebrafish model that shares common pathological pathways with humans and may be used to identify putative pharmacological targets of diabetes. Additionally, we have previously identified several candidate genes with altered expression in T2DM zebrafish. Here, we performed a small-scale zebrafish screening for these genes and discovered a new therapeutic target, centromere protein X (CENPX), which was further validated in a T2DM mouse model. In zebrafish, cenpx knockdown by morpholino or knockout by CRISPR/Cas9 system ameliorated overfeeding-induced hyperglycemia and upregulated insulin level. In T2DM mice, small-interfering RNA-mediated Cenpx knockdown decreased hyperglycemia and upregulated insulin synthesis in the pancreas. Gene expression analysis revealed insulin, mechanistic target of rapamycin, leptin, and insulin-like growth factor 1 pathway activation following Cenpx silencing in pancreas tissues. Thus, CENPX inhibition exerted antidiabetic effects via increased insulin expression and related pathway s. Therefore, T2DM zebrafish may serve as a powerful tool in the discovery of new therapeutic gene targets.