Abstract citation ID: gfae069.498

#972
A Novel Single Compound from Chinese Herbs as a Potential Candidate for Reducing obesity induced diabetic nephropathy via ATF3-RARRES1 axis pathway

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Background and Aims: Billions of people have obesity induced diabetic nephropathy. Promoting the browning of white adipose tissue has been suggested as a potential strategy for, but a drug still needs to be identified.

Method: First, WT and ATF3 knockout mice fed a high-fat diet were treated with STZ to determine that ATF3 plays an important role in obesity-induced diabetic nephropathy. Second, DBA mice fed a high-fat diet were infused with STZ, and db/db KO mice were fed a high-fat diet, and the two mouse models were injected intraperitoneally with or without the ATF3 inducer ST32da (the structure is a single drug designed based on the traditional Chinese medicine Salvia miltiorrhiza). After about one and a half months, all related kidneys function values were measured.

Results: After analysis the relationship between ATF3 and diabetic nephropathy in human GEO DataSet Browser indicated that the gene expression of ATF3 was lower in patients groups. Genetic deletion of activating transcription factor 3 (ATF3−/−) in mice under a high-fat diet (HFD) and STZ treatment resulted in more aggravated nephropathy phenomenon syndrome including higher urine albumin, lower creatinine clearance and high risk in death. ST32da, a synthetic ATF3 inducer isolated from Salvia miltiorrhiza, promoted ATF3 expression to downregulate inflammatory genes and ameliorated foot process effacement resulting in reduced diabetic nephropathy by suppressing the podocyte apoptosis via interleukin (IL)-6 and retinoic acid receptor responder protein 1 (RARRES1) axis.

Conclusion: Our study identified the ATF3 inducer ST32da and Salvia miltiorrhiza extraction, may as a promising therapeutic drug for treating diet-induced obesity induced diabetic nephropathy.