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Orai1 channel inhibition protects podocyte injury in BTBR ob/ob Diabetic Mouse Kidneys

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Objectives:

Diabetic nephropathy (DN) is a representative disease that accounts for about half of chronic kidney disease (CKD). Renal fibrosis is known to be the most important pathological change in DN. Deregulation of the Ca^{2+} signal has been implicated in the development of DN, directly and/or indirectly. Store-operated Ca^{2+} entry (SOCE) is the primary Ca^{2+} entry mechanism in the non-excitable cells including podocytes and is proposed as a potential therapeutic target for DN. Recently, it is reported that the blockade of SOCE protects podocytopathy by restoring its structural and functional changes. Here, we examined whether the Orai1 inhibitor exerts therapeutic effects in leptin-deficient BTBR *ob/ob* mouse, a well-established type II diabetic mouse model.

Methods:

Orai1 inhibitor (GSK7975A) was introduced via an osmotic minipump for 4 weeks, and a saline osmotic pump was used for the vehicle. Glomerular tuft area and mesangial matrix (by Methenamine silver stain), and podocyte density (by immunohistochemical staining with WT1) were quantified by image analyzer and compared among groups. Glomerular basement membrane (GBM) thickness was analyzed by electron microscopy.

Results:

Orai1 inhibitor significantly reduced mesangial matrix in the BTBR *ob/ob* mice compared with that of saline-treated or untreated BTBR *ob/ob* mice. Podocyte density was diminished in BTBR *ob/ob* mice, and was significantly ameliorated by Orai1 inhibitor administration (Fig.1). Furthermore, GBM thickness was also decreased in Orai1 inhibitor-treated BTBR *ob/ob* mice compared to that of saline infusion.

Conclusions:

Taken together, our data demonstrate that the blockade of Orai1 activity may restore the pathologic changes of DN in BTBR *ob/ob* mouse, and proposed Orai1 as a novel therapeutic target for DN.