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Effect of *Lactobacillus reuteri* GMNL-263 treatment on renal fibrosis in diabetic rats

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Hyperglycemia is the most important factor in the progression of renal fibrosis in diabetic kidney. Prevention and treatment of renal fibrosis may improve diabetic nephropathy. To explore whether probiotic *Lactobacillus reuteri* GMNL-263 treatment was linked to altered hyperglycemia-mediated renal fibrosis in diabetic kidney, the mechanisms of *L. reuteri* GMNL-263 treatment responsible for the inhibition of renal fibrosis in streptozotocin (STZ)-induced diabetic rats were examined. Diabetic rats were induced by intraperitoneal injection of STZ (50 mg/kg). Induction of diabetes was confirmed by measurement of the blood glucose using the glucose oxidase method, and hyperglycemic rats with levels >16 mmol/L were used. We found that *L. reuteri* GMNL-263 treatment caused reduction of glycated hemoglobin and blood glucose levels in STZ-induced diabetic rats for 28 days (all $p<0.05$). Treatment with *L. reuteri* GMNL-263 increased body weight but decreased kidney weight in diabetic rats as compared to diabetic control ($p<0.05$). In diabetic renal cortex, the Janus kinase 2/signal transducers and activators of transcription 1 (but not extracellular signal-regulated kinase/c-Jun N-terminal kinase/p38 mitogen-activated protein kinase) activation was markedly blocked by *L. reuteri* GMNL-263 treatment. The ability of *L. reuteri* GMNL-263 treatment to inhibit renal fibrosis was verified by the observation that it significantly decreased protein levels of plasminogen activator inhibitor-1, $p21^{Waf1/Cip1}$, α-smooth muscle actin, and fibronectin in diabetic renal cortex. The results obtained in this study indicate that *L. reuteri* GMNL-263 treatment may protect STZ-induced diabetic rats from hyperglycemia-enhanced renal fibrosis.

[**Key words:** *Lactobacillus reuteri* GMNL-263; Streptozotocin-induced diabetes; Renal fibrosis; Diabetic nephropathy]

Intestinal flora has been shown to influence human health in many studies (1,2). The best control of the flora balance in the intestine is achieved by the intake of probiotics, which is thought to be effective in lifestyle-related diseases (1–4). Several health beneficial effects are associated with the intake of lactic acid bacteria, including alleviation of lactose intolerance, immune enhancement, therapeutic effect on diarrhea, and the prevention of colon carcinogenesis, and atherosclerosis (3–6). In recent years, it has been reported that lactic acid bacteria have efficacy relating to the progression of diabetes (7–9). However, the mechanism underlying this finding has not been elucidated.

Hyperglycemia is the most important factor in the progression of diabetic nephropathy (DN) (10,11). Early alterations in DN include glomerular hyperfiltration, glomerular and tubular epithelial hypertrophy, and the development of microalbuminuria, followed by the development of glomerular basement membrane thickening, accumulation of mesangial matrix, and overt proteinuria, eventually a leading cause of glomerulosclerosis and end-stage renal disease (ESRD) (12,13). Excessive deposition of extracellular matrix (ECM) in the kidney is the hallmark of diabetic renal fibrosis (12–15). In DN, the extent of tubulointerstitial fibrosis is the leading cause of ESRD; fibrosis is well correlated with renal dysfunction.

Although the etiology of renal fibrosis in DN is not fully understood, much attention has focused on the role of high glucose *per se* (10,16,17). Hyperglycemia sharply increases the production of reactive oxygen species (ROS), which play a key role in renal fibrosis in DN (18,19). Recently, several mechanisms have been proposed for the oxidative damage during chronic hyperglycemia including glucose autoxidation, synthesis of advanced glycation end-products, and mitochondrial ROS overproduction (20–22). Hyperglycemia and ROS may induce changes in cellular function by common intracellular signaling pathways. Excess generation of mitochondrial ROS due to hyperglycemia initiates a vicious circle by activating stress-sensitive pathways such as Janus kinase (JAK)/signal transducer and activator of transcription (STAT), nuclear factor-κB (NF-κB), protein kinase C (PKC), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) (11,12,19,23). In general, the cellular events include increased flux of polyols and hexosamines, generation of advanced glycation end-products, increased activity of PKC, transforming growth factor-β (TGF-β)-Smad-MAPK and G-proteins, altered expression of cyclin kinases and their inhibitors, and of matrix degrading enzymes and their inhibitors with a conceivable common signaling denominator as ROS and a final outcome of increased synthesis and deposition of ECM (11,24–26).

Abbreviations: α-SMA, α-smooth muscle actin; DN, diabetic nephropathy; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; JAK2, Janus kinase 2; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; PAI-1, plasminogen activator inhibitor-1; STATs, signal transducers and activators of transcription; STZ, streptozotocin.

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